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HOMEOPATHY: A FRONTIER IN MEDICAL SCIENCE
EXPERIMENTAL STUDIES AND THEORETICAL FOUNDATIONS

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TEXT without figures

Chapter 4

4. ANIMAL STUDIES AND LABORATORY RESEARCH

The idea that at least some of the principles of homeopathy can be subjected to experimental vetting is making headway both in the homeopathic setting and among researchers in the biological, immunological, and biochemical fields. Evidence obtained for the first time in actual experiments in animals, or in isolated organ systems, or in cells *in vitro* has been accumulating in recent years [Kollerstrom, 1982; Guillemain *et al.*, 1987; Poitevin, 1988a; Poitevin, 1988c; Bastide, 1989; Fisher, 1989; Rubik, 1989; Bellavite, 1990a; Poitevin, 1990; Bastide, 1994; Righetti, 1994].

The crucial role which research studies in *in vivo* and *in vitro* experimental models can play in the phase of the development of homeopathy is universally recognized. Studies of this type, in fact, free themselves of the philosophical and methodological constraints of classic homeopathy and become part and parcel of the scientific paradigm dominant today. In this context, if the research studies are conducted with correct methods and yield results which are reproducible in different laboratories, then they cannot be refuted on the basis of arguments such as the placebo effect or simply dismissed as being inexplicable.

4.1. Experiments in animals and in healthy human subjects

As in conventional research, animal models are also used in the field of homeopathy both for testing the principle of dilution/dynamization and for studying the possible mechanism of action of homeopathic remedies in a thorough and repeatable manner, as well as for discovering remedies to be used in the veterinary context.

In this chapter we report on some of the main studies conducted in this field. We wish to point out that the fact that we refer to such studies does not imply that we endorse or support them. Moreover, we are fully aware of the problems associated with certain animal studies and hope that such research be performed only when strictly necessary and avoiding inflicting unnecessary suffering or torture upon the animals.

In toxicology, an attempt has been made to investigate whether high dilutions of a toxic substance are capable of modifying either its elimination or its consequences. A number of studies have demonstrated that a seven hundredth or 7c dilution (approximately 10^{-14} M, in terms of molar concentration) of arsenic and bismuth is capable of increasing the urinary elimination of these same metals by rats intoxicated with them

[Lapp *et al.*, 1955; Wurmser and Ney, 1955; Cazin *et al.*, 1987]. The arsenic had no effect on bismuth intoxication and vice versa, indicating specificity of action.

This property has not been observed with lead, in that high dilutions of this metal failed to modify the excretion kinetics of lead in rats [Fisher *et al.*, 1987]. The arsenic experiments have been repeated more recently using more updated and controlled methods [Cazin *et al.*, 1991]; the results were substantially the same: intraperitoneal injections of arsenic (as arsenic trioxide, As_2O_3, or arsenic acid, H_3AsO_3), diluted and dynamized, reduced the blood levels, and increased the excretion of arsenic in rats treated with high doses (10 mg/kg) of arsenic trioxide. In a series of dilutions tested (5c, 7c, 9c, 11c, 13c, 15c, 17c, 19c, 21c, 23c, 25c, 27c, 29c, 31c), the most active dilutions in the protective sense were 7c and 17c, and the difference versus dilutions of dynamized water alone was highly significant. It is of interest to note that the protective effect of the high dilutions was abolished if they were subjected to heating to 120 degrees for 30 minutes.

On the basis of the analogy existing on both the biological and anatomico-pathological planes between carbon tetrachloride (CCl_4) intoxication and phosphorus intoxication, the Bildet group have demonstrated the protective effect of high dilutions (7c and 15c) of phosphorus and of the 7c dilution of carbon tetrachloride on CCl_4-induced toxic hepatitis in the rat [Bildet *et al.*, 1975; Bildet *et al.*, 1984a; Bildet *et al.*, 1984b].

The effect of high dilutions of CCl_4 confirmed similar data reported in the nonhomeopathic literature, testifying to an increased resistance of the liver after treatment with low doses of a toxic agent [Ugazio *et al.*, 1972; Pound *et al.*, 1973]. It has also been reported that small doses of cadmium reduce the renal toxicity caused by that metal in the rat [Bascands *et al.*, 1990]. It is likely that a synthesis inducing mechanism (of so-called *stress proteins*) or a mechanism increasing the enzyme activity of the detoxification systems may play some role in this type of phenomenon.

According to the findings of another group of researchers (published in the form of preliminary results), the mortality of rats treated with lethal doses of α-amanitine (the poison of the mushroom *Amanita phalloides*) is significantly slowed (in the sense of protection in the early days after administration of the poison) by treatment of the rats with 15c dilutions of α-amanitine, *Phosphorus*, and rifampicin [Guillemain *et al.*, 1987]. According to these authors, the use of these substances in the therapy of liver intoxication corresponds to the homeopathic rationale of curing disease by means of small doses of the same poisonous substance, as in the case of amanitine, or of substances with similar toxicity in the more general sense of the term. Phosphorus is known to be hepatotoxic at high doses, whereas rifampicin may be similar to amanitine in terms of mechanism of action (inhibition of enzymatic activity such as that of RNA polymerase). Results have recently been reported bearing witness to a protective effect of *Phosphorus* 30c on fibrosis of the liver caused by chronic administration of CCl_4 in rats [Palmerini *et al.*, 1993]; the therapeutic effect of *Phosphorus* was also documented as a decrease in serum hepatic enzymes compared to a group of untreated rats.

In another study [Cambar et al, 1983; Guillemain *et al.*, 1984], a nephrotoxicity model was used: rats treated with 9c and 15c dilutions of *Mercurius corrosivus* (corrosive sublimate) were significantly protected, in terms of reduced mortality, against the toxicity of medium-to-high doses (5-6 mg/kg) of mercury.

A well-defined protocol of experimental carcinogenesis in rats has been utilized to test the effect of highly diluted carcinogens and tumor promoters on the development of carcinomas caused by high doses of the same agents [De Gerlache and Lans, 1991]. Briefly, a large percentage of rats which received in their diet 2-acetylaminofluorene (0.03% for 21 days) and phenobarbital (0.05% for 12 months) developed hepatocellular carcinomas after 9-20 months. Treatment of the animals with 2-acetylaminofluorene 9c or with phenobarbital 9c (added to the drinking water, where the final concentration was about 2×10^{-19} M) significantly reduced and delayed the development of liver tumors with respect to a control group which received only the solvent diluted and dynamized. The authors concluded that this is the first reported observation of a significant effect obtained with treatments of this nature on a large experimental basis, even if these results need further confirmation by other experimentalists to be fully demonstrative.

According to the research by Cier and coworkers [Cier *et al.*, 1966] in the mouse, the administration of *Alloxan* 9c partly inhibits the diabetogenic effect of a dose of 40 mg/kg of alloxan. This effect was obtained both with preventive and curative (i.e. after the diabetogenic injection) administration.

The observation that high dilutions (7c-9c) of bee venom (currently used in homeopathy for skin manifestations with edema, erythema, and itching) had a protective and roughly 50 percent curative effect on X-ray-induced erythema in the albino guinea-pig [Bastide *et al.*, 1975; Poitevin, 1988b; Bildet *et al.*, 1990] appears to confirm the principle of similarity of reaction which underlies homeopathy. Bee venom, which at

high doses (bee stings) causes edema and erythema, is capable, at given dilutions, of curing an edema or an erythema caused by some other agent. The fact that such results are in agreement with biological studies on isolated cells, demonstrating that *Apis* 7c (crushed bee) blocks the activation of basophils *in vitro* is significant (see Chapter 4, Section 3).

Following the same line of studies, the effect of homeopathic preparations of histamine on edema of the foot in the rat, induced by the injection of inflammatory doses (0.1 mg) of histamine, has been investigated. Using this model, a small, but significant inhibitory effect of high dilutions of histamine (up to 30x), administered intraperitoneally to rats 30 minutes before and at the same time as histamine injection in the paw, was noted [Conforti *et al.*, 1993].

Another series of studies examines the action of high dilutions of silica on the production of platelet activating factor (PAF) by peritoneal macrophages in the mouse [Davenas *et al.*, 1987]. The compound was added to drinking water at the 9c dilution (corresponding to a theoretical concentration of 1.66×10^{-19} M) for 25 days. The peritoneal macrophages extracted from the mice thus treated showed a PAF production capability in response to a stimulus with yeast extracts which was 30 to 60 per cent greater than that of control macrophages (untreated mice, mice treated with NaCl in 9c dilution or with another homeopathic drug, *Gelsemium* 9c). Lower dilutions (5c) paradoxically had less effect.

Homeopathic dilutions of silica are widely used in homeopathy for the treatment of sores, chronic ulcers, and abscesses. An experimental model in animals, based on the repair of holes pierced in the ears of mice, was used by a group of investigators in Rehovot (Israel): they reported that high dilutions of silica (up to 200c), added to drinking water for 4-20 days according to the particular experiment, heal the lesions faster and bring about a greater reduction in their size than sodium chloride solutions used as a control [Oberbaum *et al.*, 1991; Oberbaum *et al.*, 1992].

Bastide's group [Doucet-Jaboeuf *et al.*, 1982; Doucet-Jaboeuf *et al.*, 1984; Bastide *et al.*, 1985; Doucet-Jaboeuf *et al.*, 1985; Bastide *et al.*, 1987; Guillemain *et al.*, 1987; Daurat *et al.*, 1988] have shown the immunostimulatory effect in mice of endogenous compounds such as thymic hormones and interferons prepared in high dilutions according to homeopathic procedures. Among the many experiments reported, particularly worthy of note are those describing the effects of high dilutions of α-β interferon ($8\text{-}16 \times 10^{-10}$ IU i.p.) and thymic hormones (8×10^{-8} pg i.p.) on parameters of humoral (number of plaque-forming cells) and cellular (allospecific cytotoxic T-cell response) immunity. The authors then suggested that to achieve good therapeutic efficacy in immunodepressed patients these immunity mediators might be used in extremely low doses [Bastide *et al.*, 1985].

From the studies conducted by this group, another interesting result emerges to illustrate one of the most significant problems of homeopathic research: the pathophysiological state of the experimental animal powerfully conditions the results of any given treatment. This prompted the investigators to assess the effect of homeopathic dilutions (from 4c to 12c) of thymus and thymuline on mice of The Swiss strain, considered immunologically normal, and mice of the New Zealand Black (NZB) strain, considered immunologically depressed. The treatment caused significant immunostimulation only in the NZB mice, whereas the Swiss mice underwent immunodepression (particularly marked with the dilutions of thymus) [Guillemain *et al.*, 1987; Daurat *et al.*, 1988].

Other findings worthy of note in the field of immunomodulatory research are those reported by Bentwich and coworkers [Weisman *et al.*, 1991; Bentwich *et al.*, 1993]. After previously demonstrating that very small amounts (6c and 7c dilutions) of KLH (hemocyanin) antigen are capable of specifically modulating the antibody response in experimental animals [Toper *et al.*, 1990], they repeated and expanded on the experiments by showing the immunomodulatory effects of homeopathic dilutions of the antigen in mice. The animals were preconditioned for 8 weeks with i.p. injections of dynamized dilutions of KLH antigen (from 10^{-14} M to 10^{-36} M) and of saline (control). They were then regularly immunized with KLH dissolved in complete or incomplete Freund's adjuvant. Serum levels of specific antibodies were determined by immunoassay and the results showed a significant increase in specific IgM response with all the preconditioning dilutions, as well as a significant increase in specific IgG response in animals pretreated with KLH 10^{-36} M. The authors conclude that extremely small amounts of antigen are enough for specific immunomodulation and, in particular, that homeopathic dilutions beyond the Avogadro constant still have some effect. The authors, however, acknowledge that in view of the vast implications of these findings, these experiments must be rigorously repeated and confirmed.

Another interesting point to emerge from the experiments in animals has to do with the importance of the chronological factor: a given treatment will be perceived differently by the organism depending upon the

time of day (circadian rhythm) or the month of the year (circa-annual rhythm). This variability and its possible biological consequences have been examined by various authors [Cambar and Cal, 1982; Doucet-Jaboeuf *et al.*, 1984; Cambar and Guillemain, 1985; Guillemain *et al.*, 1987; Ibarra, 1991]. It is well known that chronobiology is today a frontier area also for conventional biomedical research [Minors, 1985; Breithaupt, 1988].

Another team of researchers have reported that homeopathic preparations of zinc in decimal dilutions (from 4x to 12x, corresponding to amounts of zinc ranging from 0.025 mg to 0.25 pg), administered to rats for seven days consecutively, significantly increased the release of histamine by peritoneal mastcells [Harish and Kretschmer, 1988].

Other data appear to indicate that two substances with similar actions can interfere with each other's effects when one of the two is used in a homeopathic dilution as an "antidote" to the other [De Caro *et al.*, 1990]. Repeated i.p. injections of isoproterenol or of the tachykinin eleidosin give rise, within the space of a fortnight, to a substantial increase in size of the salivary glands, which return to their normal size within 30 days of discontinuation of the treatment. Isoproterenol was administered i.p. as a stimulant of the glandular response (100 mg/kg for a fortnight), whereas eleidosin was given i.p. in dynamized dilutions ranging from 10^{-10} to 10^{-426} g/ml to assess whether or not it was capable of preventing the increase in size of the gland, if given earlier, or of accelerating its return to normal, if given after treatment with isoproterenol. Both responses were significantly different as compared to controls, revealing that low dynamized doses of eleidosin not only produce an action opposite to that of high doses, but also counteract the action of a substance which has similar effects on animals.

A team of American researchers have reported the results obtained with very high dilutions of mice tissues infected with *Francisella tularensis*, in practice a preparation of a nosode of tularemia [Jonas *et al.*, 1991]. They produced the dynamized dilutions from reticulo-endothelial tissue of mice infected with tularemia, obtaining three dilutions containing original tissue (3x, 7x, 12x) and three dilutions beyond the presence of original tissue (30c, 200c, 1000c). These preparations were administered orally to a group of mice, whereas another control group was treated with dilutions of ethanol. An LD_{50} or LD_{75} of *F. tularensis* was then administered and survival time and total mortality were evaluated. After 15 experiments the very high homeopathic dilutions brought about a significant increase in survival time and a significant reduction in total mortality compared to controls. The protection did not correlate with the level of dilution, number of shakings, or presence or absence of original tissue. The authors conclude: "We could not confirm our hypothesis that preparations diluted beyond the level of remaining organisms behaved identically to controls in the prophylaxis of infectious challenge. These findings should be repeated, confirmed by other investigators, and evaluated further" [Jonas *et al.*, 1991, p. 21].

Researchers from the Department of Zoology of the University of Kalyani (India) worked on radiation-induced damage [Khuda-Bukhsh and Banik, 1991; Khuda-Bukhsh and Maity, 1991]. The experimental protocol consists in irradiation of albino mice with 100-200 rad of X-rays (sublethal doses) and evaluation, after 24, 48, and 72 hours, of cytogenic damage such as frequency of chromosomal aberrations, formation of micronuclei, and the mitotic index. In this system, the possible radioprotective effects of homeopathic drugs such as *Ginseng* 6x, 30x, and 200x and *Ruta graveolens* 30x and 200x (rue), administered orally before and after irradiation, were tested. The results reported would appear to be highly significant, in the sense that the mice treated with the homeopathic remedies suffered significantly less damage than the control mice (irradiated and treated with dilutions of ethanol). Significantly, the authors, though defining this protective action as "spectacular," conclude that it is very difficult to explain the precise mechanism whereby such alterations due to the homeopathic drug may be possible at such high dilutions *in vivo* [Khuda-Bukhsh and Banik, 1991].

Interesting and sound are the studies conducted by Sukul and coworkers of the Department of Zoology of the University of Santiniketan (India) [Sukul *et al.*, 1986; Sukul, 1990; Sukul *et al.*, 1991; Sukul *et al.*, 1993]. These studies consist in numerous experiments conducted in rats, mice, and cats. Amongst other things, the authors report that the homeopathic drugs *Gelsemium* (yellow jasmine), *Cannabis indica* (Indian hemp), *Graphites* (graphite), and *Agaricus muscarius* (toadstool), administered orally (as granules dissolved in a small amount of water) to albino rats, significantly increase the catalepsis induced by motor blockade (a nervous disorder which sets in when rats are repeatedly forced to remain immobile) [Sukul *et al.*, 1986]. The effect of these drugs, in 30c and 200c dilutions, was comparable to that of well known conventional drugs such as pilocarpine and aloperidol administered in ponderal doses (5 mg/kg). The effects were assessed in

comparison with rats receiving granules of lactose without active drug. The 200c dose appears to have a longer duration of action than the 30c dose.

The same research team is currently working on another interesting model which may provide important indications with regard to the mechanism of action of homeopathic remedies. In a recent communication [Sukul *et al.*, 1993], the authors report that potentized homeopathic drugs applied to the tongues of rats evoke electrophysiological responses of the hypothalamic neurons. Rats kept on a high-salt diet were anesthetized and a microelectrode, connected up to an oscilloscope, was implanted in the lateral hypothalamic area to record the discharge frequency in that area. After a suitable period recording the basal tracing, a few drops of *Natrum muriaticum* (sodium chloride or common sea salt) were deposited on the tongues of the rats. The application caused marked changes (reductions) in the discharge frequency of the nerve center. This experiment suggests both that the action of the drug can be mediated by the hypothalamic nerve centers and that preconditioning with a high-salt diet makes the animal more sensitive to the remedy *Natrum muriaticum*.

Cuprum (copper) is used in homeopathic therapy as a spasmolytic agent. A French team [Santini *et al.*, 1990] have developed an animal model for assessing the possible effect of *Cuprum* on digestive motility. A 4c solution of this remedy (corresponding to roughly 10^{-10} M) was administered (0.3 ml i.p.) to mice, which then received treatment with neostigmine at ponderal doses (50 μg/kg), a drug which accelerates intestinal motility. The parameter measured was the distance travelled by phenolsulfonphthalein in the intestine. The results showed that the homeopathic treatment significantly reduces the effect of neostigmine, bringing the intestinal transit rates back to values closer to those recorded in mice not treated with neostigmine.

Homeopathy is also finding applications in veterinary medicine. For instance, there has been a report on a study conducted in dairy cows showing that the remedy *Sepia* (cuttlefish ink), at the 200c dilution, significantly reduces a number of typical postpartum complications [Williamson *et al.*, 1991] and another on a study conducted in pigs showing that various combinations of *Lachesis* (venom of the bushmaster snake), *Pulsatilla* (windflower), and *Sabina* (savin) or *Lachesis*, *Echinacea* (coneflower), and *Pyrogenium* (artificial sepsin), associated with *Caulophyllum* (blue cohosh) (all in low dilutions, from 1x to 6x) have prophylactic and therapeutic effects on infections (metritis and mastitis) of sows and on diarrhea of piglets [Both, 1987].

The development of the immune system of the chicken is stimulated by a homeopathic hormone dilution [Yubicier-Simo *et al.*, 1993; Bastide, 1994]. In this study, bursectomy was performed in chick embryos, making them immunodeficient (it is well known that the bursa of Fabricius is essential for the development of the B lymphocyte system in this animal). "*In-ovo*" administration of low doses and high dilutions of the hormone bursin (up to 10^{-30} - 10^{-40} g/ml), theoretically no longer containing any molecules of the original substance, restores the immune response, as demonstrated by normal antibody production on the part of the adult animal in response to antigen stimulus (bovine thyreoglobulin). Moreover, an improvement in the response of the pituitary-adreno-cortical axis has been seen, as shown by measuring adrenocorticotropic hormone.

Lastly, some mention should be made of a number of recent studies published by the research group coordinated by Endler [Endler *et al.*, 1991a; Endler *et al.*, 1991b; Endler *et al.*, 1994a; Endler *et al.*, 1994b]. In these studies, two Austrian laboratories (Graz) and one Dutch laboratory (Utrecht) demonstrated that extreme dilutions (30x) of thyroxine (T_4) are capable of significantly inhibiting ($p < 0.01$) the metamorphosis of tadpoles and also the spontaneous tendency of young frogs to leave the water. It should be noted that thyroxine at ponderal doses accelerates the metamorphosis. The tests were conducted in the course of dozens of experiments comparing parallel dilutions of thyroxine with dilutions of solvent (water). The quality of these experiments is borne out by the fact that the solutions used for the tests were coded by an independent researcher and the codes were broken only at the end of the experiments, thus constituting a blind procedure, which is rarely used in conventional research in animals. This experimental model has proved very versatile for the purposes of establishing optimal procedure, time, and dosage conditions for achieving the best results; amongst other things, it has been demonstrated that significant effects appear as little as a few minutes after exposure of the animals to the thyroxine dilution.

As regards the research of Endler and coworkers, it is worthy of note that these studies were conducted according to criteria of nonviolence to animals, without causing them any physical harm, and allowing them to return to their natural habitats after completion of the experiments.

In this section, we should also mention a number of experimental studies conducted in healthy human subjects, inasmuch as they are not clinical trials as such to assess the therapeutic efficacy of a drug, but actual experiments aimed at identifying its possible mechanism of action. These experiments may also be classified

within the framework of the classic homeopathic *provings*, which for some years now have been conducted on a double-blind, placebo-controlled basis. There are a certain number of reports of this type in the literature, showing that homeopathic drugs taken repeatedly by healthy subjects cause particular symptoms and even variations in physiological parameters detectable in the laboratory [Julian, 1979; Smith, 1979; Campbell, 1980; Bayr, 1986; Nagpaul, 1987; Koenig and Swoboda, 1987; Vakil *et al.*, 1988]. The effect on healthy subjects would appear to be particularly pronounced in hypersensitive subjects, i.e. not all individuals respond to homeopathic test doses [Poitevin, 1988a].

There have also been reports, in official hematological journals, of a paradoxical effect of acetylsalicylic acid: in healthy volunteers, homeopathic dilutions of aspirin (2 ml of 5c dilution, corresponding to approximately 0.000000002 mg by sublingual administration) caused a statistically significant reduction in bleeding time ($p < 0.05$) compared to placebo (distilled water) [Doutremepuich *et al.*, 1987a; Doutremepuich *et al.*, 1987b; Doutremepuich *et al.*, 1988; Doutremepuich *et al.*, 1990]. Since it is well known that aspirin causes an increase in bleeding time at pharmacological doses (50-500 mg), the findings of these studies may possibly be interpreted as a demonstration of the law of similars. Nevertheless, the mechanism whereby this happens is still unclear because, while we know that aspirin at normal doses exerts its action by inhibiting the function of platelets, in the work by Doutremepuich it is reported that "homeopathized" aspirin has no effect on platelet aggregation [Doutremepuich *et al.*, 1990].

4.2. Studies in isolated organs

Aubin's team [Aubin, 1984; Pennec and Aubin, 1984] have conducted pioneering studies on the cardiotoxic activity of aconitum and veratrum, both of which are substances used in homeopathy. At low dilutions (high concentrations) (10^{-5} M) aconitum caused fibrillation in the isolated perfused heart; at medium dilutions (10^{-7} M) it caused bradycardia; at high dilutions (10^{-18} M) it had no effect on the healthy heart, but on the heart pretreated with low dilutions of aconitum it had a distinct protective effect normalizing rhythm and other signs of cardiotoxicity. Similar results were obtained with veratrum [Pennec *et al.*, 1984a; Pennec *et al.*, 1984b]. These experiments appear to confirm the efficacy of high dilutions in cells and tissues somehow sensitized or predisposed by pathological situations.

Benveniste and coworkers [Hadji *et al.*, 1991; Benveniste, 1994] reported results obtained with an experimental model consisting in isolated perfused guinea-pig heart (Langendorf system). The coronary flow of these hearts increased with infusion of very high dilutions of histamine (above 30x), as normally occurs with the normal low dilutions. The infusion of buffer alone (control) or of a high dilution of methylhistamine (inactive histamine analogue) did not alter coronary flow. Assays were done in "blind" conditions. The vasodilatory activity of histamine in very high dilutions was destroyed by treatment at 70°C for 30 minutes or as a result of exposure to a magnetic field of 50 Hz for 15 minutes. The authors concluded that water, deprived of the solute by serial dilutions, retains a specific activity which can be suppressed by means of physical treatments which in themselves have no effect on the solute.

The isolated perfused guinea-pig heart model appears to be very effective for this type of study and to furnish reliable results. In point of fact, in two later publications [Benveniste *et al.*, 1992; Litime *et al.*, 1993], Benveniste's group reported that the system is also sensitive to immunization-dependent activation. On immunizing the animals (guinea-pigs) with ovalbumin and taking the heart for the experiment between the 9th and 20th day, an increase in coronary flow could be achieved at very high dilutions (10^{-31} - 10^{-41} M) of ovalbumin.

Fragments of oat seedlings (coleoptiles) during the rapid growth phase were cultured in the presence of the vegetable growth factor indoleacetic acid. In these conditions, pretreatment with homeopathic dilutions of $CaCO_3$ (5c) caused a statistically significant increase in growth compared to coleoptiles treated with indoleacetic acid alone [Bornoroni, 1991]. It is interesting to note that the author suggests a possible mechanism of action of the $CaCO_3$ dilution, namely that it may increase the concentration of extracellular Ca^{2+} and thus act in synergism with indoleacetic acid in activating the H^+-K^+ pump (which causes cellular acidification and an increase in proliferation), or it may promote better uptake of the Ca^{2+} present in the culture medium and thus increase cell activation.

Doutremepuich's team, who conducted the study on aspirin at high dilutions in healthy human subjects (see Chapter 4, Section 1 above), have also published reports on cultures of vascular fragments and blood platelets [Lalanne *et al.*, 1990; Lalanne *et al.*, 1991; Lalanne *et al.*, 1992; Doutremepuich *et al.*, 1993]. The

platelet aggregation rate is slowed and its overall proportions reduced by the presence of fragments of vascular wall in the incubation medium. This phenomenon is well known and is probably due to the production of a number of physiological mediators. The authors cited have shown that a homeopathic preparation of high dilutions of aspirin (5c) inverts the inhibitory effect of the vascular fragments and thus, in practice, restores the previously inhibited platelet aggregation to normal; the result constitutes *in vitro* confirmation of the findings reported in healthy human subjects, where highly dilute aspirin reduces bleeding time.

We are familiar with the fact that beta$_2$-agonists (isoproterenol, salbutamol, tulobuterol) cause relaxation of tracheobronchial muscle. A recent report [Callens *et al.*, 1993] shows that these agents are capable of inducing relaxation of basal tone, in a model of isolated guinea-pig trachea, even at high dilutions (from 10^{-20} M to 10^{-36} M, in dynamized decimal dilutions).

4.3. Studies in *in vitro* cells

The most significant studies have been conducted on human basophils, using the degranulation test [Benveniste, 1981; Sainte-Laudy, 1987; Cherruault *et al.*, 1989]. This test investigates the metachromatic property of these cells, using an optical microscope for the basophil count. Benveniste's team have demonstrated that this phenomenon is due to changes in membrane transport rather than to actual degranulation [Beauvais *et al.*, 1991], but here the phenomenon will be treated as *degranulation*, using the term adopted in the early studies. The first publications on the effect of high dilutions on basophils [Poitevin *et al.*, 1985; Poitevin *et al.*, 1986] report that the *in vitro* degranulation induced by various allergens (house dusts, mites) was inhibited by high dilutions of bee venom (*Apis mellifica* 9c and 15c). A later study [Poitevin *et al.*, 1988] examined basophils stimulated with anti-IgE serum, analyzing the effect of two products used in the homeopathic treatment of allergic syndromes, *Apis mellifica* and *Lung histamine*. These drugs yielded significant inhibition at theoretical concentrations of 10^{-9} M and 10^{-17} M. On examining the dose-effect relationship, an alternation of inhibition, inactivity, and stimulation was observed, giving rise to a *pseudosinusoidal* trend. Inhibition was then obtained with high dilutions of pure histamine, with inhibition peaks around 6-7c and 17-18c [Poitevin *et al.*, 1988; Poitevin, 1990]. Since the effects observed seem to depend on histamine and melittin (the main components of bee venom), the authors suggested as possible mechanisms of action the nonspecific blockade of IgE, or the regulation of phospholipase activity (melittin is known to activate phospholipase A2), or the negative feedback of histamine on its release.

A multicenter study under the guidance of Jacques Benveniste, conducted in collaboration with four other laboratories, has reported that human basophils are sensitive to infinitesimal doses of substances which are already known to have a stimulatory effect at ponderal doses, such as anti-IgE antibodies, calcium ionophores, or phospholipase A2. The specificity of action has been corroborated by the lack of effect of other ultradiluted substances such as anti-IgG antibodies (basophils, in fact, are activated only by anti-IgE antibodies) and phospholipase C, which has a different biochemical specificity on the membranes [Davenas *et al.*, 1988]. The dose-response curves showed that decreasing doses were accompanied first by disappearance of activity, then by its reappearance and then by various alternating activity peaks and inactivity troughs up to very high dilutions, corresponding to practically zero antibody concentrations (Figure 1). It is also reported that in order to obtain maximum activity at the infinitesimal dilutions the dilution process needed to be accompanied by vigorous succussion (10 sec. with a vortex) and that the stimulatory activity of the diluted antibody solutions persisted even after ultrafiltration through membranes with a pore size of less than 10 kDa, which should have retained the antibody out of solution.

Figure 1. Basophil degranulation in relation to increasing dilutions of anti-IgE antibody. (From Davenas *et al.*, 1988, by courtesy of Macmillan Magazines Ltd.)

Given that these experiments represent a key issue in discussions on homeopathy, they need to be examined in depth, and a number of precise points need to be made. The work of Benveniste's research team, published in the authoritative scientific journal, *Nature*, has aroused a great deal of interest as an alleged

practical demonstration of the "*memory of water*," but was fiercely criticized both on theoretical grounds (the "unbelievable" nature of the data) and on account of difficulties relating to the repeatability of the results and methodological shortcomings (a kind of inspection was organized by *Nature* in Benveniste's laboratory) [Lasters and Bardiaux, 1988; Maddox *et al.*, 1988; Pool, 1988].

Such strongly critical and sometimes downright sarcastic or ironic stances do not appear entirely justified: the concept of the "memory of water" is no more than *a metaphor denoting the hypothesis whereby the physicochemical properties of water can be modified by a solute and remain so for a certain period of time even in the absence of the solute itself*. If this were true, biology, and medicine would undergo not a revolution, but certainly a significant increase in knowledge and in the related applications. It is not a matter here of postulating an "entity" (memory) which may reside in the water, conferring upon it cognitive and mnemonic properties, but of studying the physicochemical properties of water itself. In this sense, talking about memory is not so very different from talking about temperature, dielectric constants, viscosity, and other properties.

An example may serve to clarify the concept outlined here: if we take a little water and put it in the freezer, after a certain amount of time it will freeze. On removing the water from the freezer, it will be observed that the block of ice, though now exposed to room temperature, will remain a block of ice for some time. Thus, there exists in water a property which enables it to "remember" for a certain amount of time that it has been kept in the freezer. For those who find this example self-evident, we can give another: if we take a tape coated with ferric hydroxide and subject it, as it is running, to a series of differences in potential in precise succession, changes in charge occur on the magnetic substrate; the tape will remember these changes for hundreds of years. It is not the memory of water, in this case, but the memory of iron, which consists in a *particular form* that the magnetic substrate assumes on the tape.

To our mind, the attempt to repeat an experiment regarded as interesting and important is the only position which may be considered scientifically correct and useful. Recently, the Benveniste group repeated the tests according to more reliable methodologies and more complete statistical assessments, confirming the existence of an effect of high dilutions, though not as striking as those reported in the first study published in *Nature* [Benveniste, 1991a; Benveniste *et al.*, 1991a; Benveniste *et al.*, 1991b]. The issue has therefore still to be resolved on the experimental plane.

The "Benveniste affair" is a typical example of scientific misrepresentation. Most people today simply believe that Benveniste has been proved wrong and that the issue is closed. This does not correspond to the facts. In the first place, if we take the trouble to read the documentation in *Nature*, we note that a panel consisting of a magician, a journalist, and an expert in statistics were invited to witness a number of experiments in the course of a week, most of which (though not all) yielded negative results, and therefore the panel produced a totally negative report based on various arguments, but largely ones which the researchers of the host laboratory had good grounds for refuting [Benveniste, 1988]. Clearly, this type of experiment will meet with reproducibility problems, due both to ignorance of the physical basis of the phenomenon and thus of the environmental and experimental factors capable of influencing it, and to the particular methodology, which is based on semiquantitative assessments using a microscope. What is quite unacceptable, however, is that a group consisting of three nonexperts in the field should feel entitled to demolish in one week more than two years' work in a laboratory which is celebrated throughout the world for its studies on mastcells.

The data reported in the above-mentioned paper in *Nature* are open to criticism of a procedural type in certain respects, but all the major lines of scientific research have had their teething problems in terms of methodology and even interpretation. The pillorying of the Benveniste group, as the editorial board of *Nature* went out of their way to do, bears all the hallmarks of a political maneuver and has precious little in common with a true scientific debate. That this is so is borne out by the fact that Benveniste's latest studies have been greeted by the scientific community with total silence. No serious criticism has been forthcoming. It is as if the new data had not even been published, and the public at large is left with the idea that the memory of water is merely a figment of the imagination. But this, as Benveniste sees it, is not a scientifically valid way of going about it: "There are only two possibilities:" - he writes in a comment - "either the data is wrong and it must be shown to be wrong; or it is right and represents a most important discovery in biology, which not only legitimizes the high dilution/agitation effect used in homeopathy, but also reaches to the core of any biological process - molecular communication. The problem therefore needs to be known and experiments need to be performed; international cooperation needs to be extended so that these important results and their implications be fully recognized" [Benveniste, 1991b]

A Dutch group have reported that they failed to reproduce the effect of high dilutions of IgE [Ovelgonne *et al.*, 1991; Ovelgonne *et al.*, 1992]. In their study it proved impossible to demonstrate any action of high dilutions of anti-IgE antibodies on mastcells, and the authors (one of whom had learnt the technique in Benveniste's laboratory) conclude that it is a model which is very hard to reproduce. Similar findings have also been reported by another group of investigators, who published on *Nature* [Hirst *et al.*, 1993]. However, the latter work has been criticized for a number of methodological discrepancies by the Benveniste's team [Benveniste *et al.*, 1994a] and also the report of Ovelgonne *et al.* is open to various interpretations as concerns the possible existence of "vortex-related" effects [Wiegant, 1994]. As a matter of facts, Fred Wiegant is probably right when he writes in a letter to *Nature* that in this story "the last word has not yet been spoken" [Wiegant, 1994].

A French team have investigated the effect of various homeopathic drugs, particularly homeopathically diluted histamine, on basophil degranulation (observed under the microscope) [Cherruault *et al.*, 1989; Boiron and Belon, 1990]. The inhibitory activity of progressive centesimal dilutions was evident with activity peaks alternating with ineffective dilutions. The main activity peaks were achieved at the 7c, 17c, 28c, 39c, and 51c dilutions. All the experiments were performed blind, in the sense that the experimenter did not know which dilution he was working with. A control group received histidine dilutions, which proved ineffective, thus reducing the possibility that the results might have been artefacts.

The Sainte-Laudy and Belon group reported further data confirming the fact that high dilutions of histamine (pure histamine chloride) significantly inhibit the degranulation of basophils (sensitized with IgE antibodies to the dermatophagoid) induced *in vitro* by dermatophagoid extracts. In a series of 16 progressive centesimal dilutions (from 5c to 20c), the authors observed histamine inhibitory activity in dilutions of around 7c and 18c. The addition of pharmacological doses of cimetidine (an H_2-receptor antagonist) abolished the effect of all the active dilutions. The authors therefore are inclined to believe that H_2-receptors are involved in the action of the high dilutions, though they admit that "it is paradoxical to think in terms of molecular biology when theoretically there are no molecules of the effector in some of the active dilutions tested" [Sainte-Laudy *et al.*, 1991, p. 136]. Recently, the same group published a study conducted blind with rigorous statistical analysis, demonstrating that the activation of human basophils by IgE is strongly and significantly inhibited ($p < 0.001$) by dilutions of histamine [Sainte-Laudy and Belon, 1993]. In these experiments, two main inhibition peaks were obtained, the first with dilutions from 10^{-16} to 10^{-22} M, and the second with dilutions from 10^{-28} to 10^{-36} M.

Along the lines of the toxicity tests performed in animals (see above) Boiron's group [Boiron *et al.*, 1981] reported that mercuric chloride ($HgCl_2$) at minimal doses (5c) protects fibroblast cultures from intoxication by high doses of mercury. The parameter studied was the mitotic index. Others [Mansvelt and Van Amons, 1975] observed a cytotoxic effect of $HgCl_2$ on cultured mouse lymphocytes at doses from 10^{-5} to 10^{-7} M, whereas a growth inhibiting effect, without cytotoxicity, was observed at doses from 10^{-16} to 10^{-17} M. This effect, however, was not found by another group studying the action of dilutions ranging from 10^{-10} to 10^{-18} M on the same model [Kollerstrom, 1982].

We know that cadmium, an environmental pollutant, and cisplatin, a cytostatic drug used in antitumor therapies, have marked effects on the kidney tubules. It has been reported that the pretreatment of (5-day) kidney cell cultures with very low doses (10^{-16} M) of cadmium and cisplatin has a protective effect against the toxicity caused by medium-to-high doses (10^{-5} - 10^{-6} M) of these substances [Delbancut *et al.*, 1993].

A Montpellier University research team has shown the effect of epidermal growth factor (EGF) on the proliferation of cells in culture (lines of human keratinocytes and fibroblasts). EGF at very low doses (10^{-19} M) and in high dilutions (10^{-45} M) caused significant effects on these cells, in the sense that it reduced the growth of the keratinocytes and stimulated that of the fibroblasts [Fougeray *et al.*, 1993].

Two papers reporting on the effect of *Phytolacca* (pokeroot) on lymphoblastic transformation appear to be of particular interest [Colas *et al.*, 1975; Bildet *et al.*, 1981]. *Phytolacca* contains a glycoprotein, the mitogenic *Pokeweed*, which is known to induce the lymphoblastic transformation of B lymphocytes in culture. *Phytolacca* has also been used empirically in homeopathy for some years now (since before its immunological action *in vitro* was known) in numerous conditions involving adenopathy, such as, for instance, infectious mononucleosis and viral disease in ORL [Mossinger, 1973; Poitevin, 1988c]. In resting lymphocytes, 5c, 7c, and 15c dilutions of *Phytolacca* have no mitogenic effect, but in lymphocytes stimulated with ponderal doses of phytohemagglutinin (PHA) they exert a 28 to 73 percent inhibitory effect on mitosis (maximum effect by the 15c dilution in one study [Colas *et al.*, 1975], and by the 7c dilution in another [Bildet *et al.*, 1981]. What emerges forcefully once again in these experiments are the concepts of

biological tropism (whereby an ultradiluted solution has an activity which is directed against the same target system as the undiluted substance) and of inversion of effects (whereby the dilute solution inhibits the effect of the original substance or of a substance similar to it).

A study of the action of succussed substances on human lymphocytes stimulated with phytohemagglutinin (PHA) and on PMN granulocytes stimulated with opsonized zymosan (OZ) was conducted by a team led by Olinescu in Bucharest [Chirila *et al.*, 1990a and 1990b]. From peripheral blood of patients allergic to bee venom or immunodepressed (cancer) patients PMN granulocytes and lymphocytes were isolated, and the stimulatory index was assessed following PHA (tritiated thymidine test) for the lymphocytes, or production of O_2^- after OZ (chemiluminescence test) for the granulocytes. Before being stimulated the lymphocytes were incubated in a medium supplemented with various dilutions of bee venom and the granulocytes with various dilutions of cortisol (2c, 7c, 14c, 30c). As controls, a number of cells were supplemented with succussed or nonsuccussed distilled water. It was found that the lymphocytes of allergic patients were inhibited in their proliferative response by the high dilutions of the venom (7c, 15c, 30c). The inhibition was not observed in the controls supplemented with succussed and nonsuccussed water. The immunodepressed patients had low lymphocyte stimulatory indices, both in the presence and in the absence of dilutions of bee venom. As regards the production of O_2^- by PMN granulocytes stimulated with OZ in the presence of diluted cortisol, different responses are reported compared to controls, both stimulatory and inhibitory, though the data were not statistically significant. According to the authors, the data obtained suggest a possible effect of succussed dilutions on the structures of the cell membrane.

Other studies have also been conducted on phagocyte cells (polymorphonuclear leukocytes and macrophages). In this case, substances were tested which are used in homeopathy in situations in which there is acute inflammation with a strong polymorphonuclear component. An inhibitory effect of *Belladonna* (deadly nightshade) and of *Ferrum phosphoricum* (phosphate of iron) at dilutions of 5c and 9c has been reported on the production of oxygen free radicals (chemiluminescence) induced by opsonized zymosan [Poitevin et al., 1983]. The inhibition was highly significant and got up to approximately 30-40%, roughly the same degree of inhibition obtained with 10^{-6} M of dexamethasone and 10^{-4} M of indomethacin. Simultaneously, *Apis mellifica* (crushed bee) was tested, but no changes were found. The authors point out that there is a substantial difference in individual sensitivity to these drugs. This problem of the differing sensitivities of cells isolated from different subjects has also been stressed by others [Moss *et al.*, 1982], who investigated the effects of *Belladonna* (deadly nightshade), *Hepar sulphur* (Hahnemann's calcium sulfide), *Pyrogenium* (artificial sepsin), *Silicea* (silica), and *Staphylococcinum* on chemotaxis, obtaining contradictory results. This latter study has been criticized [Poitevin, 1988a] on the grounds that the solutions used in the tests were not sterile, which might account for the variability of the results.

It has also been reported (in a preliminary communication) that *Bryonia* 4c and 9c (wild hops) had a stimulatory effect on the oxidative metabolism of polymorphonuclear leukocytes, which may be both direct and indirect (increasing the response to chemotactic peptides) [Fletcher and Halpern, 1988].

Since in our own laboratory we currently use a method for the measurement of the functionality (in terms of production of superoxide anion and adherence) of the white blood cells, particularly the neutrophils, a similar approach has been adopted to that of Benveniste's group, attempting to activate these cells with solutions of agonists or antagonists diluted according to the homeopathic method. Our results [Bellavite *et al.*, 1991a] have been largely negative, in the sense that the cell activities undergo the influence of compounds tested in a range of dilutions from 4x to 10x, and thus in conditions in which the doses were similar to those commonly used in conventional research. It should be stressed, however, that Benveniste, too, attempted to test high dilutions on neutrophilic granulocytes and platelets, with negative results (personal communication).

Another approach to the study of the action of homeopathic drugs on cell systems in our laboratory consisted in the evaluation of the effects of homeopathic preparations on human neutrophils in culture, activated with formylated peptides [Bellavite *et al.*, 1991b; Chirumbolo *et al.*, 1993]. The results of this research, based on analysis of an extensive series of compounds and of several dilutions, can be summarized as follows:

a) *Manganum phosphoricum* 6x and 8x (phosphate of manganese), *Magnesia phosphorica* 6x and 8x (phosphate of magnesia), *Acidum citricum* 3x (citric acid, and *Acidum succinicum* 3x and 4x (succinic acid) had significant and reproducible inhibitory effects on the neutrophil's oxidative metabolism.

b) *Acidum fumaricum* (fumaric acid) and *Acidum malicum* (malic acid), both at the 4x dilution, had slightly potentiating effects.

c) *Phosphorus* and *Magnesia phosphorica* often presented inhibitory effects, in the course of the various experiments, even at very high dilutions (greater than 15x), but these effects did not always appear at the same dilutions, thus making any statistical assessment of the phenomenon a difficult matter.

These results lend themselves to multiple interpretations as to the possible reasons for the effects observed from the biochemical point of view. In the first place, they go to show that the solutions used have determined effects on blood cells at medium-high doses. Moreover, the data appear to suggest that most of the remedies tested act in such a way as to interfere with subtle regulatory mechanisms of the cell, notoriously based on ion exchanges and on phosphorylation and oxido-reduction processes. In fact, in normal cell physiology, elements of major importance in these mechanisms are phosphorus, sulphur, magnesium, manganese, calcium, and others.

Wagner's group [Wagner, 1985; Wagner, 1988; Wagner *et al.*, 1988; Wagner and Kreher, 1989], have experimentally tackled the problem of the effect, at cell level (i.e. on leukocytes), of low doses of vegetable extracts used in homeopathy and, in addition, of the unusual changes in effect observed in the dose-response curves. Among the various studies produced by the group, of particular interest are those which report that the naphthoquinones (plumbagin, alkannin, and others) and cytostatic agents (vincristine, methotrexate, fluorouracyl) at relatively high concentrations (100 µg - 10 ng/ml) inhibit, whereas at very low concentrations (10 pg - 10 fg/ml) they stimulate lymphoblastic transformation and granulocyte phagocytosis. Intermediate doses are ineffective. The authors have suggested that a number of antitumor effects of vegetable extracts might be explained by this dose-related double-effect mechanism.

Reports have been published on various experiments on vegetable cells. These include particularly interesting papers which demonstrate that pre-treatment with homeopathic dilutions of toxic substances (e.g. $CuSO_4$) protect vegetable cells against the intoxication induced by medium-to-high doses of the toxic substance itself [Guillemain *et al.*, 1984; Guillemain *et al.*, 1987].

4.4. Preliminary conclusions from experimental studies

The experimental studies referred to in this section bear witness to the existence of a form of homeopathic research, about which normally very little is known. There are now many groups operating throughout the world (and above all in Europe) who have started to set themselves the task of experimentally demonstrating the truth or falsity of certain “sacred” principles of classic homeopathy, on the basis of the tenets of modern biological research. Of course, as has been done in the case of clinical research, there is no lack of critics who quite rightly subject many of the papers published - mostly in journals not ranking among the most prestigious in the field - to highly demanding methodological vetting and expose their serious shortcomings. It cannot be denied that most of what we read, particularly apropos of the effects of ultradiluted solutions, still awaits corroboration by independent research teams.

When discoveries threaten to undermine the foundations of pharmacology, or, at any rate, suggest the need for new theories, they must be corroborated by evidence which in terms of methodology and reproducibility is superior to the common standard, and not inferior to it, as, unfortunately, is all too often the case in this field. We have already mentioned the problem of how difficult it is to reproduce the spectacular results of certain laboratories. This problem, whose *raison d'etre* lies in our virtually total ignorance of the possible mechanism of action of the ultradiluted homeopathic solutions, is destined to remain the major stumbling-block in the path of all those coming to grips with this difficult and challenging area of research. If the effect of solutions which are practically devoid of molecules of the active compound exists, it is necessarily of nonmolecular type, and thus lies beyond the scope of any normal quality control of the solutions used in the experiments.

A critical review of the entire literature on research in homeopathy has been attempted in the past [Scofield, 1984] and is currently under way in certain university settings [Linde *et al.*, 1991; Linde *et al.*, 1993]. Linde's work reviews 109 publications reporting on 106 different studies, 82 of which conducted in animals, 14 in plants, 6 in isolated organs, and 5 in cell cultures. Practically all the papers reviewed report positive results, at least at certain dilutions. In particular, the dilutions most frequently found to have demonstrable effects are 5c and 9c. According to rigorous criteria the quality standards were judged to be poor, especially on account of the shortage of information on the methods used in preparing the dilutions, on the composition of the mother tinctures and on chronobiological details. Only about 30 percent of the studies obtained a score better than 50 percent of the maximum according to the analysis by Linde and coworkers.

The authors conclude that, judging only on the basis of methodologically satisfactory studies, there is distinct evidence of the efficacy of very low doses and high dilutions, but that to date too few research protocols have been reproduced by independent teams.

Needless to say, poor reliability does not mean falsification. The need for caution with regard to the reliability of research which has yet to be reproduced in different laboratories is mandatory in any case, but what we have said does not mean that part of the research conducted to date, and perhaps even a substantial part, is not valid. There remains an increasingly urgent need for experimental studies to be amplified and intensified, particularly within the framework of first-class research centers, for funds to be allocated to the teams involved in the research and for the ostracism to cease at university level in relation to anyone and anything associated with homeopathic medicine.

On the whole, then, the mounting body of laboratory experiments over recent years is beginning to provide useful information, which, alongside the more traditional and less easily controlled reports of clinical practice, enables us to draw a number of conclusions:

a) The studies cited in this section appear to demonstrate the existence of biological activity of drugs at medium and high dilutions prepared according to the standard practices of homeopathy. With reference in particular to research on high dilutions (beyond the Avogadro constant), there can be no doubt that a certain amount of difficulty or slowness emerges in reproducing results unequivocally and in a statistically significant manner.

b) Owing to the uncertainty regarding the real nature of homeopathic drugs, laboratory research has so far done very little towards clarifying its mechanism of action.

c) In many cases it would seem that there is a certain consistency between the starting hypotheses, based on experience and on the homeopathic rationale (law of similars, opposite action of high dilutions compared to the toxic effect of the substance itself) and the results achieved in animals, in healthy human subjects, and in experiments *in vitro*. A certain substance which is pharmacologically active when tested in highly diluted solutions appears to react specifically to the same biological system to which the nondiluted substance reacts [see, for example, Wurmser and Ney, 1955; Bildet *et al.*, 1984; Aubin, 1984; Bastide *et al.*, 1985; Taylor Reilly *et al.*, 1986; Doutremepuich *et al.*, 1987; Davenas *et al.*, 1988; Poitevin, 1988a; Poitevin *et al.*, 1988; Vakil *et al.*, 1988; Doutremepuich *et al.*, 1987a]. The homeopathic cure is thus thought to be due to a *biological tropism* for specific receptor systems. We can therefore postulate, though only speculatively, that the signal transmitted by the highly diluted solution is recognized specifically by the target system and processed in a particular way.

d) The reaction to the high dilution is often the opposite of that observed at low dilutions; a compound can have a protective action against the toxic effects of the same or other compounds; a pro-inflammatory agent may present anti-inflammatory effects at high dilutions [Bildet *et al.*, 1975; Bildet *et al.*, 1981; Boiron *et al.*, 1981; Bildet *et al.*, 1984; Cazin *et al.*, 1987; Guillemain *et al.*, 1987; Poitevin, 1988a; Wagner *et al.*, 1988; Bastide, 1989; Doutremepuich *et al.*, 1990; Bildet *et al.*, 1990; Delbancut *et al.*, 1993]. It should be noted, however, that this inversion of effect is not a constant feature [Mansvelt and Van Amons, 1975; Doucet-Jaboeuf *et al.*, 1984; Bastide *et al.*, 1985; Davenas *et al.*, 1988; Harish and Kretschmer 1988; Hadji *et al.*, 1991; Fougeray *et al.*, 1993], and therefore must not be considered a universal rule with regard to the action of homeopathic drugs, but merely as a possibility which comes about when suitable reactivity conditions exist in the system tested. This aspect, which is of substantial importance for the understanding of homeopathy, will be analyzed more specifically in Chapters 5 and 6 which relate the mechanism of action of the homeopathic remedy to the cybernetic complexity of cellular and systemic homeostasis.

The biological and perhaps also the therapeutic efficacy of drugs at low or very low doses might be due to the fact that the alteration of physiological systems during disease predisposes them to changes in sensitivity at specific receptor level, this being something with which classic pharmacology is also thoroughly familiar [Brodde and Michel, 1989]. The fact that a specific reactivity state should be reached for ultra-low doses to be efficient has been clearly shown also on *in vitro* model systems [Lalanne *et al.*, 1992].

The effects of homeopathic-type drugs might therefore be explained (and this explanation is meant to serve only as an initial working hypothesis) in two ways: the drug stimulates a number of biological mechanisms which are inhibited or blocked by exogenous or endogenous pathogenetic factors, or the drug inhibits a response mechanism which is activated in a disproportionate or distorted manner by the agent causing the disease. This aspect will be discussed in greater detail in Chapter 6.

Nevertheless, many studies on highly diluted solutions suggest that the type of information and signal conveyed by these solutions differs, at least in certain respects, from those known to classic biology and

pharmacology. The fact that many experiments show that the effect increases, or remains stable, or oscillates between an increase and a decrease, during successive dilutions suggests that some specific type of information of a compound at homeopathic doses may be activated or amplified by the dilution and succussion process. This may therefore be interpreted as biological activity in the presence of traces of molecules or even in their absence, and on the strength of this the term "*metamolecular biology*" has been coined [Davenas *et al.*, 1988].

The precise nature of this phenomenon remains unknown, but clearly the explanation should be sought in the particular physicochemical behavior of the solvent (water, or water with various percentages of ethanol) during the dilution and succussion process. The particular characteristics of aqueous solutions of highly diluted compounds will be addressed in greater detail in Chapter 7.

4.5. Towards new paradigms

In the foregoing paragraphs we have seen that some measure of support or explanation, or at least the start of an explanation, can be found for many of the empirical observations present in the homeopathic tradition within the framework of the modern biological, biochemical, and immunological sciences. In particular, the plausibility of the law of similars and the possibility of pharmacological effects at increasingly low doses are confirmed, if not as "laws" endowed with universal validity, then at least as properties peculiar to living systems, the importance of which went unrecognized up until only very recently. From here we have still a very long way to go before we can claim that the scientific basis of homeopathy has been explained. To say that the law of similars is plausible does not mean that we have explained its mechanism of action. Moreover, the problem of the effects of very high dilutions still remains substantially unsolved.

We have seen that there are a considerable number of research studies suggesting the existence of some form of biological activity of highly diluted solutions, which is therefore of a different type from that commonly known. If the scientific community is to definitively accept this phenomenon, which would unquestionably usher in a completely new phase in the study of biology and medicine, the evidence will have to be even stronger in terms of repeatability and its applicability to various different experimental models. Nevertheless, the sum of the clinical observations (see Chapter 3) and the experimental findings (see Chapter 4) is beginning to prove so extensive and intrinsically consistent that it is no longer possible to dodge the issue by acting as if this body of evidence simply did not exist. It must be admitted, however, that there is still no model providing any satisfactory or adequate explanation as to what type of information is contained in the high homeopathic dilutions, where theoretically there is a total lack of molecules of the active ingredient.

The empirical evidence *per se* fails to provide any kind of explanatory hypothesis. At this point, then, the process of reasoning, based as ever on what is known to be scientifically certain (or at least reliable), should grind to a halt due to a lack of "fuel" or "raw material." Since, however, the aim of this book is not merely to provide an updated overview of the literature on homeopathy, but, above all, to formulate new hypotheses serving both as stimuli and guidelines for further research, the problem needs to be tackled from a broader-based viewpoint than that inspiring the individual research efforts presented. For this reason, reference will be made to a vast body of evidence and theory that science has come up with in fairly recent years. The evidence and theories discussed here are not immediately related to the study of homeopathy, but refer to the functioning of biological systems and to the physicochemical principles underlying nature. It is only in this way that a hypothesis can be constructed on sound foundations.

We have entitled this "broadening of the horizons" of the scientific viewpoint "*towards new paradigms*," inasmuch as any attempt to come to grips with the scientific basis of homeopathy must necessarily figure within the framework of a distinct change in our present way of conceiving science and medicine. The difficulty the academic world has in accepting homeopathy is not primarily of a scientific nature, but rather is epistemological [Attena, 1991]. The problem is not just the weakness of the scientific evidence, or the lack of any explanation of the mechanism of action: both of these drawbacks apply to the study of new and old conventional drugs as well. Whether a new therapy is efficacious or not is a common and thoroughly legitimate question in the modern medico-scientific setting, and in this latter context no-one would dream of protesting against drugs of very dubious efficacy being investigated or even experimented with in patients (obviously, once their nontoxicity has been proven). Moreover, medical practitioners are well aware that we do not know the precise mechanisms of action of many drugs, including some of the most common ones.

Thus, the problem of the acceptance or otherwise of homeopathy lies on a different plane, where what matters is the "philosophical" conception of science (epistemology). To get a clearer idea of what this means it is worthwhile dwelling for a moment or two on the concept of a *scientific paradigm*.

One of the most important keys to interpretation in our present approach to the evolution of science and therefore of medicine is our view of the history of scientific theories as a discontinuous succession of paradigms. *A paradigm is a set of theoretical assumptions, experimental practices, and modes of transmitting the contents of science* [Kuhn, 1962; Arecchi and Arecchi, 1990]. It therefore constitutes a frame of reference common to scientists in a certain period, in which theories, models, methods, instruments and, above all, a certain type of language form a single, coherent whole. Seen from the inside, a paradigm may present such coherence and demonstrative strength that any contradictions prove negligible. Those who operate within the framework of a given paradigm base their efforts on a model which is accepted by all, whether it be in conceptually designing research protocols, in choosing methodologies, or in drawing conclusions from experimental results. In this way it proves much easier to obtain research funds (projects appear very logical and important to funding agencies) and to get one's work published in the leading scientific journals (the language used and the conclusions drawn come up to the expectations and understanding capability of the scientific community).

Certainly, one factor with a decisive impact on the development of a paradigm is the economic and technological situation, the evolution of which sometimes enables researchers to make veritable leaps forward in their research in quality terms. David Ruelle, for instance, a member of the French *Académie des Sciences*, writes: "Contemporary international science tends to be confused with American science. It is undoubtedly true that research (and good research) is also done elsewhere, but the United States dictate fashions and how things are done" [Ruelle, 1992, p. 75]. The predominance of North American high technology and spending power is an objective consideration which inevitably has repercussions on the way science is conducted.

The type of relationship existing between the various paradigms in a given age, or between paradigms succeeding one another in history is still a subject of heated debate among epistemologists. According to some, paradigms are struggling among themselves for a sort of supremacy, and forcibly oust one another in successive "revolutionary breaks with the past." According to others, the progressive evolution and transformation of one paradigm into another is possible without dramatic clashes or contradictions, at least on the scientific plane.

From time to time in the course of the history of medicine various different paradigms have gotten the upper hand. In primitive or pre-scientific societies the paradigm dominating the study of natural phenomena was based on philosophy or mythology; later, in western countries, with the development of anatomical techniques and physiological investigations, a more descriptive and classificatory approach was adopted (1600-1700); in the next phase, the medical world went over to a paradigm based on the cell, with the advent of cellular pathology and microbiology (1700-1800); lastly, in the wake of the enormous advances made in chemistry and biochemistry, we come to the present-day paradigm which can be defined as molecular. Molecular biology today appears to be the interpretative basis for all cellular and pathophysiological phenomena, even going so far as to embrace neuronal and psychic events. The explanation of disease processes, whether genetic or acquired, is sought and, where possible, located in mechanisms consisting in quantitative and/or qualitative modifications of particular molecules making up part of the various anatomical or physiological systems.

Today, however, in the very heyday of the molecular paradigm, we are witnessing signs of a change in tendency, or at least signs of substantial variations on the molecular theme. There are now many people who perceive the inadequacy of the molecular paradigm when it comes to coping with major health problems such as neoplastic, degenerative, autoimmune, endocrine-metabolic, and neuropsychiatric disease. This inadequacy is not quantitative, since no-one would deny the importance of making further progress in our knowledge of the molecular mechanisms involved in these diseases. The problem is another: the sheer quantity of notions, the growth of which is exponential, cannot be mastered even by the specialists in the various disciplines, and brings in its wake a progressive sub-specialization in various sectors. The pursuit of a unitary approach, capable of assuring a multidisciplinary synthesis and of defining the nature of disease processes at higher levels of organization, is proving increasingly difficult. In practice, though not in principle, this ongoing accumulation of notions and data proves inadequate as a means of furthering our understanding of complex vital phenomena and thus of the phenomena relating to health and disease. The

word *complexity* is appearing with increasing frequency in scientific articles dealing with genetics, cell communication systems, and metabolism.

It makes no sense for us to react to this situation by denying the importance of the molecular approach, of which all modern biomedical practitioners are a more or less conscious expression; what makes much more sense is to respond by initiating exploration in other territories, within other paradigms, in order to see what new things they may have to offer. As often happens in operations taking place in uncharted territory, the people conducting the exploration are exposed both to the incomprehension of those who are used to keeping "both feet firmly on the ground" and to the real risk of taking the wrong path or going up blind alleys. What justifies the enterprise, from the point of view of the explorers, is basically scientific curiosity, the innate urge which prompts human beings to make new discoveries. What diminishes the foolhardiness of embarking on new and uncertain paths is the possibility of orientation and guidance provided by the scientific method, which so far has proved capable of bearing the brunt of the investigative effort, regardless of whether one is operating within the framework of one paradigm or another. The basis and origin of the experimental method is *observation*, often the product of chance or accident, but always meticulously and scrupulously recorded; this develops into a series of reasoned arguments and ideas which generate an *explanatory theory*, which in turn enables us to formulate hypotheses to be submitted to *experimental* testing. As long as experiments can be performed, we are authorized to construct hypotheses, however fanciful or outlandish these may be. Ideas and hypotheses, Karl Popper maintains, may originate in the researcher's mind perhaps as inspired guesswork or as the sudden illumination of a series of items of knowledge long imprinted on the mind, or even as the result of character traits or inclinations. What really matters is that these hypotheses can be tested and that they may be subject to invalidation.

A new paradigm enables previously inexplicable phenomena to be explained scientifically and previously unsolvable problems to be solved and therefore it becomes increasingly important, the greater the social and economic relevance of the phenomena concerned. It has been claimed that any paradigm inevitably reflects the cultural climate and economic situation of the period in which it is developed. In this day and age, when, despite the enormous scientific progress of biomedicine, an increasing number of people are turning (rightly or wrongly) to other forms of therapy, when conventional drugs are beginning to prove highly expensive both for the national health service and the patient's pocket, increasing pressure is being brought to bear for a change in attitude towards previously neglected therapies.

Homeopathy, by its very nature, presents a challenge to the molecular paradigm, or rather, to the claim the molecular paradigm sometimes makes that it is the only way of interpreting biological reality. A better place for homeopathy might be within the framework of a new paradigm emerging in medicine, which might be defined the *biophysical paradigm*. Molecules are not the only decisive factors, inasmuch as energies and information of an electromagnetic type, used so far, and only partially, for diagnostic purposes (ECG, EEG, NMR, X-rays, evoked potentials) may play a major role. The same concept has been clearly expressed by Beverly Rubik, director of the Center for Frontier Sciences at Temple University, at a recent GIRI conference: "The observations of low dose biological effects challenge the dominant paradigm of mechanical reductionism, of viewing life as a collection of biomolecules responding to molecular stimuli. The enhanced potency of very low doses as in homeopathy appears to challenge molecular theory, one of the pillars of the modern chemistry. On the other hand, it may demonstrate that something else is occurring at these very low doses that does not involve molecules" [Rubik, 1994, p. 162].

According to other views, it would be more appropriate to set homeopathy squarely within the framework of the *complexity paradigm*. In this perspective, the dynamic interrelationship between the various components of the human being, ranging from the physico-anatomical to the mental, is highlighted, as is that between human beings and their environment. The homeopathic "diagnosis" and therapy are addressed primarily at the whole person as a single unit (the homeopathic *simillimum* is at the same time an analysis and a synthesis of all the aspects of dysregulation encountered in the patient), rather than at the anatomico-functional lesion and the individual symptom. For this reason, some people see homeopathy as a form of medicine that cures the whole patient and not just the disease.

These two different interpretations of nature and homeopathy, oriented towards biophysics and complexity, respectively, do not clash head on, but rather serve to illustrate the novelty and up-to-date topical nature of the homeopathic approach. Within the context of these two lines of thought, one should perhaps be able to view from the right perspective and perhaps even overcome the difficulties which homeopathy and other forms of so-called alternative medicine, such as those of the oriental tradition, meet with in their struggle to establish themselves and gain acceptance.