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ORIGINAL PAPER

Classical and new proving methodology: Provings of *Plumbum metallicum* and *Piper methysticum* and comparison with a classical proving of *Plumbum metallicum*

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Objective: **To study the reliability of a proving methodology and the reproducibility of proving symptoms.**
Methods: **Two homeopathic medicines and placebo were given, in a double-blind randomized design, to 31 healthy volunteers (13 *Piper methysticum* 30C, 11 placebo and 7 *Plumbum metallicum* 30C), 5 drops 4 times daily, until the onset of unbearable symptoms, or at most for 1 week. The primary outcome measure was the number of phrases containing unusual or new symptoms selected by supervisors (SEL) from unstructured diaries and the number of these symptoms (SYM) present in SELs. The secondary outcome measures were the number of symptoms with modalities of both verum groups concordant with symptoms reported in a previous proving of *Plumbum* 12C. Other parameters evaluated were repeated and crossed symptoms in SELs.**
Results: **Both medicines showed qualitative and quantitative differences from placebo. *Piper*: 146 SELs (median: 5), *Plumbum:* 118 SELs (16), placebo: 48 SELs (2), containing 260 (8), 199 (29) and 58 (2) SYMs, respectively. There was a significant difference from placebo in *Plumbum* but not in *Piper* SELs and SYMs ($P<0.05$). 31, 24 and 4 'repeated' and 18, 22 and 2 'crossed' symptoms were found in *Piper*, *Plumbum* and placebo. 8 and 30 symptoms concordant with the classical proving of *Plumbum* were found for *Piper* and *Plumbum*, corresponding to about 10% and 45% of their total SELs.**
Conclusions: **Open diaries, supervision and double-blind placebo are useful methods in homeopathic pathogenetic trials. Estimates of concordance should be introduced in proving methodology.** *Homeopathy* (2005) **94,** 164–174.

Keywords: proving; homeopathic pathogenetic trial; selected notes; concordant symptoms; repeated symptoms; crossed symptoms; *Plumbum metallicum*; *Piper methysticum*

Introduction

Homeopathic provings or pathogenetic trials [1] are the most important method to determine the pathogenetic effect of substances for homeopathic use and the experimental base of clinical homeopathy.[2] Several

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homeopathic provings have been published in recent years[3–5] but differing methodologies were used. Hahnemann's method is described in detail in his 'Organon',[6] but is open to interpretation, for instance concerning dilution of the remedy and its posology. Hahnemann and Kent[7,8] used frequent daily repetition, except in the case of sensitive volunteers, more recently some investigators give only a few doses, waiting for the symptoms to appear.[9] Other debates include sample size, analysis and the use of placebo control.[10,11] A recent systematic review of homeopathic pathogenetic trials in the United Kingdom from 1945 to 1995 concluded that 'inadequate use of placebo and failure to use placebo as a comparator leads to overestimation of pathogenetic effects'.[11] In fact the number of pathogenetic effects in the trials of best quality was very low compared to trials of poorer quality. The authors are sceptical that 'homeopathic dilutions can elicit at least one symptom in 75% of volunteers', but they state that if this is true, 'then controlled studies with small sample sizes followed by at least 4 weeks of follow-up would be appropriate'. A third issue of discussion is the criteria for the causality assessment of pathogenetic effects and the modalities used to select the effects. Classical provings make use of supervision with a final interview to select pathogenetic effects while some recent re-provings[12,13] used structured diaries and/or closed questionnaires but failed to identify differences between verum and placebo.

Finally, we wish to highlight the problem of succussed placebo. Many researchers think that placebo should be succussed like the verum, others consider this as part of the action of homeopathic medicine. Some recent experimental works[14–17] demonstrate that serial dilution/dynamization changes the structure of aqueous solutions, with different biochemical and biophysical properties. Succussed water may have positive or negative actions on plants[18,19] but the direction of this action is not predictable. It seems that, unlike plain water, dynamized water is active and able to change symptoms, we therefore consider the use of dynamized water as control doubtful. Some laboratory researchers on high dilution think that the control should not be dynamized and use unshaken control in their experiments.[18–20]

In three single-blind pilot studies with *Arsenicum bromatum* 30C[21], the onset of symptoms in healthy volunteers seemed different between verum and placebo. The goal of this trial was to verify the proving methodology used in pilot studies, and to investigate whether

(a) the onset of new symptoms is different in verum and placebo groups,
(b) the new symptoms are specific (similar or not to symptoms produced by other substances), and
(c) the symptoms are reproducible or not in different provings.

We conducted simultaneous double-blind placebo-controlled provings of *Plumbum metallicum* (*Plumbum*) and *Piper methysticum*. *Piper* is said to stimulate mental function,[22] while *Plumbum* slows comprehension, memory and voluntary thought.[23] Reproducibility was studied by comparing the results with a previous *Plumbum* proving, published in Hartlaub and Trinks' Reine Arzneimittellehre.[24]

Toxicology of Plumbum metallicum

Lead is an 'enzyme poison', binding to sulphydryl groups of proteins; it interferes with calcium transport, activation of brain protein kinase C, neurotransmitters synthesis, mitochondrial oxidative phosphorylation and with different ATPases. It blocks some synthetic enzymes involved in the haeme biosynthesis. Lead poisoning syndrome (Saturnism) causes abdominal spasms, digestive alterations, acute and chronic nephropathy and neurological troubles. Sub-clinical lead poisoning can cause deficits in cognitive function in children.[25]

Methods

Recruitment

The pathogenetic trial included volunteer provers, supervisors, and a director. The director recruited supervisors at meetings in Milan and Rome with homeopathic doctors from schools of homeopathy connected with FIAMO. The supervisors recruited volunteer provers at their schools. All volunteers signed a consent form. As Italian National Bioethical Committees do not consider homeopathic experimentation we did not seek approval from a bioethical committee.

Inclusion and exclusion criteria

Inclusion criteria were a complete medical history using a prepared schedule, medical qualification, absence of disease. Exclusion criteria were chronic diseases (in the past year), treatment or hospitalization (past 6 months), vaccination (past 3 months) or dental intervention (past month), severe anaemia (Hb less than 80 g/L), severe tachyarrhythmias, raised erythrocyte sedimentation rate, medication (conventional or homeopathic) in the previous 2 months (6 months above 200C or 1000K). Low homeopathic potencies (below 30C or 200K) were allowed only occasionally in the previous 2 months.

Test substances

We used a liquid preparation of the 30C dilution. The homeopathic stocks came from Laboratoires UNDA S.A. (Belgium). The final 48 bottles (30C in 43% ethanol solution) were prepared and distributed by Ce.M.O.N. s.r.l. (Grumo Nevano, Naples, Italy). An automatic machine gave 100 succussion per

dilution to 32 bottles, 16 *Piper* and 16 *Plumbum*. 16 placebo bottles were filled with the same solution of the remedy without serial dilution and succussion. Verum and placebo bottles were indistinguishable and labelled with a bottle number. To avoid electromagnetic contamination we wrapped the bottles in aluminium foil and put them in individual boxes. The medicine was taken 5 drops an hour away from food, 4 times daily, increasing to 6 times after the 3rd day, if no symptoms appeared.[27] The intake was stopped immediately if symptoms were strong, but continued in case of mild symptoms.

Study design

We conducted a double-blind, three groups, placebo-controlled proving. Diaries were kept for 3 weeks (run-in period, intake period and observation period, see Table 1). Only symptoms occurring for the first time during the second and third week were considered new, residual symptoms were observed for a further 2 months. In previous trials this posology caused the onset of symptoms within 2–3 weeks in almost all verum provers.

Randomization and blinding

Supervisors and provers were blinded to the nature and number of the homeopathic medicines used and to the proportion of placebo until the director had received the selected data (Table 1). The director had no influence in the selection of the symptoms and any discussion of symptoms between provers was forbidden. The director chose at random three bottles, one from each group, and grouped them together. Representatives of the supervisors chose at random one group of three bottles per supervisor. Randomization was thus in blocks of three to ensure even distribution of volunteers from different regions of Italy and errors of supervisors in the treatment groups.

Supervision and case taking

Each supervisor could supervise no more than 3 provers. Supervisors took a baseline medical history. A proving Record Form was used (Table 2).[27] the provers reported their daily life and events, physiological functions (appetite, sleep, digestion, and thermoregulation) and the objective state of skin and mucous membranes everyday for 3 weeks. Incomplete compilation of the Proving Form (e.g. without baseline history), illegible journal or intercurrent illness were grounds for exclusion.

Table 1 Schedule

1 month before: case-taking and selection of provers.
1st proving week: run-in period, writing of diaries (end of the week: delivery of bottles to provers).
2nd proving week: intake of the remedy, writing of the diary, telephone contact with prover.
3rd proving week: observation period, writing of diaries.
2-3 months after: meeting of supervisor and prover to select the symptoms written in the diary.
4-5 months after: delivery of diaries to director for analysis and comparison with the original proving by Hartlaub and Trinks.

Table 2 Proving Record Form

(A) 2 pages for classical anamnesis and 8 pages of symptoms under observation
(B) 1 page of instruction on observation of physiological functions, skin and month
(C) 21 pages of proving journal
(D) 1 page to sum up personal sensations and symptoms proved

Table 3 Criteria for causal association of symptoms with the tested medicine

The symptom was associated with the pathogenetic effect of the medicine if it was
● not present in the anamnesis of the last year nor in the run-in week
● judged as 'new or unusual symptom' by both provers and supervisors
● a strong aggravation or a modification of known modalities of presentation
● mentioned by the prover in the final comment

Primary outcome measure: 'Selected Notes and Symptoms'

After completion of the diaries, supervisors and provers met to select symptoms and events described as 'very unusual and/or never happened before'.[26]

Sentences containing such symptoms were called Selected Notes (SEL), listed in chronological order and used for analysis. The director compiled the SELs of each journal with their provers code, proving day and time of writing. In sentences like 'Pains the whole week', the symptom was considered present every day of the week, so the SEL was taken 7 times. Symptoms (SYM) in SELs could be only new (not in anamnesis, nor in run-in week), modified (different modalities) or returned (after 10–12 months). Aggravated symptoms were excluded except in the case of a strong aggravation; ameliorated symptoms were excluded. Dreams were considered only in qualitative analysis (repeated and crossed symptoms). Written comments of volunteers at the end of the diary were considered SELs (Table 2, point D). The criteria for selection are given in Table 3. SYMs were counted for each prover and used for statistical and qualitative analysis.

Secondary outcome measure: 'Concordant Symptoms'

Hartlaub & Trinks[24] give 1024 symptoms for *Plumbum*; we eliminated 533 toxicological symptoms comparing only the pathogenetic symptoms of *Plumbum 12c* with those of our proving. Only symptoms described in both provings with the same modalities (anatomical, chronological, kind of pain, caused by, arisen after, aggravated or ameliorated by), or with the same associated symptoms, were selected, except for mental symptoms which were accepted without modalities. These symptoms were named Concordant Symptoms. The comparison with the classical proving was performed by the director, after unblinding, in both verum groups, to evaluate specific reproducibility and was confirmed by a bilingual homeopath.

Qualitative analysis

(a) *Chronological analysis:* SELs were plotted to show the number of SELs per day for each group.
(b) *Repertory symptoms:* the symptoms of the SELs corresponding to a rubric of Kent's Repertory[28,29] were classified by chapter, except: (i) dreams were excluded, (ii) some functionally-related chapters were joined together, (iii) it was allowed to form only one symptom from a single sensation (with or without modalities).
(c) *Repeated symptoms (REPs):* REPs are symptoms recurring in at least three different SELs on at least two different days.
(d) *Crossed symptoms (CROs):* CROs are symptoms reported one or more times in at least two different diaries. Repeated and Crossed symptoms were selected independently by supervisors and confirmed by a second analysis. The results were discussed with the director to obtain a general consent.

Statistical analysis

For the statistical analysis we considered only SELs and SYMs. We used one-way analysis of variance (ANOVA) if data were normally distributed, otherwise the Kruskal–Wallis test.[30]

Results

One hundred and twenty-six doctors were asked by 18 supervisors to participate, but 79 declined or were excluded. The initial group of volunteers was 47, but only 36 provers, with 15 supervisors, started the intake of the homeopathic medicine, 34 journals were analysed and 31 were analysed for their pathogenetic effects (Table 4). Only one adverse reaction requiring interruption of treatment occurred, a *Piper* prover with severe pain and swelling of his knee. The age of the provers ranged between 29 and 50, with an average of 41.7 ± 6.3 years; there were 17 males and 14 females. For *Plumbum* the average age was 43.4; the group comprised 3 females and 4 males. In *Piper* the average age was 42.9, the group consisted of 5 females and 8 males. For placebo average age was 39.3; there were 6 females and 5 males.

Analysis of the diaries showed that during the run-in week before taking the homeopathic medicine, the sentences containing emotional or physical symptoms were 118 in the placebo group, 123 in *Plumbum*, 122 in *Piper*, without any significant difference between the groups. These symptoms persisted in approximately the same numbers in the second and third week of proving, but none were selected by supervisors, except for a few errors (see Selected Notes).

Selected Notes (SELs) and Symptoms (SYMs)

146, 118 and 48 SELs were found in *Piper*, *Plumbum* and placebo diaries, containing 260, 199 and 58 SYMs (Table 5). Three verum provers, two *Plumbum* and one *Piper*, showed a strong reaction; they decreased or temporarily stopped the intake. Another *Piper* prover developed pain and swelling of the knee and definitively stopped medication. No strong reactions were noted with placebo. Some possible errors of the supervisors during selection were noted (i.e., inclusion of run-in-period symptoms), but the number of these errors was not high (5% of overall SELs). Most of these errors were probably due to difficulty of the supervisor in judging the symptoms.

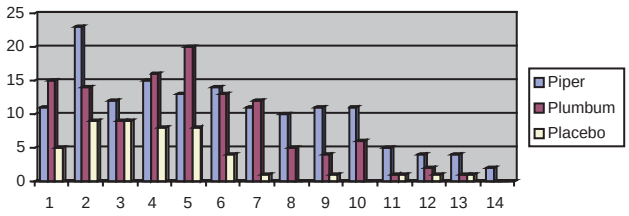
Table 4 Flow of participants (W = withdrawal, AD = acute disease, R = during run-in)

Assessed for elegibility = 126	Excluded = 79	RANDOMIZED = 47	
Remedies	Piper	Placebo	Plumbum
Allocated to intervention	16	16	15
Received allocated intervention	13	15	8
Did not receive allocated intervention	3 (2 W, 1 AD)	1 (1 W)	7 (6 W, 1 AD)
Lost out follow-up	0	1 (tonsillitis R)	1 (neuralgia R)
Analysed	13	14	7
Excluded from analysis	0	3 Use of antiinflammatory drugs Code breaking (4 SELs) Absence of baseline history	0
Included in analysis	13	11	7

Table 5 Distribution of SELs and SYMs (each number in last column represents the number of SELs/SYMs of a single prover, i.e.: 0 = a prover with 0 SELs/SYMs)

Remedies		Number of SELs/SYMs (Median)	Distribution of SELs/SYMs in different provers
Piper	$n = 13$	SELs: 146 (5) SYMs: 260 (8)	0-0-0-1-2-4-5-7-7-11-18-18-73 0-0-0-1-3-5-8-9-11-11-21-32-159
Plumbum	$n = 7$	SELs: 118 (16) SYMs: 199 (29)	3-9-9-16-17-31-33 6-11-21-29-37-47-48
Placebo	$n = 11$	SELs: 48 (2) SYMs: 58 (2)	0-0-0-0-1-2-4-5-11-12-13 0-0-0-0-1-2-4-7-14-15-15

Table 6 Distribution of SELs in the second (intake) and third (post-intake) week of proving. Horizontal axis = day; vertical = the number of SELs



Concordant symptoms

Thirty different Concordant symptoms for *Plumbum* and 8 for *Piper* were found. We found 56 different SELs containing these symptoms in *Plumbum*, and 14 in *Piper* (respectively, about 45% and 10% of their overall SELs). Symptoms 1 and 8 in *Piper* (corresponding to 2 different SELs) and 14 and 18 in *Plumbum* (corresponding to 2 different SELs) had incomplete concordance, but the underlying physiopathological meaning seems the same. The Concordant symptoms are presented in the *Appendix*.

Qualitative analysis

(a) Chronological analysis

The onset of symptoms, as it appears from the SELs, was higher during the homeopathic medicine intake period and decreased during the post-intake week (third week) (see Table 6). This phenomenon was similar but less marked with placebo. The chronological distribution of SELs with placebo shows a simple ascending–descending shape, while in verum there are more complex shapes with two or three peaks or a plateau.

(b) Repertory symptoms

Placebo showed no special localization in any chapter, while both verum groups showed a great difference from placebo in some sections (Table 7). *Piper* showed many symptoms in head and in extremities (mostly pain), while *Plumbum* showed many symptoms in mouth, digestive tract and genitals. A higher number of mental symptoms was found in verum than in placebo, while, with placebo, amelioration of mental state was frequently observed. The most important symptoms in placebo were burning pain in the stomach, eyes burning pains, mental dullness, diarrhoea, torticollis, skin eruptions and sensation of heat.

Table 7 Distribution of symptoms in different chapters of Kent's Repertory

Chapter	*Piper* n = 13	*Placebo* n = 11	*Plumbum* n = 7
Mind	51	4	32
Vertigo	0	0	2
Head	57	1	16
Eyes and vision	4	7	4
Ears and hearing	0	0	0
Nose	0	0	0
Face	7	1	3
Mouth and teeth	15	2	20
Throat/external throat	0	4	2
Stomach	11	13	11
Abdomen	6	1	9
Rectum	16	4	15
Urinary apparatus	3	1	0
Genitals M/F	2	2	14
Larynx-trachea	2	0	0
Respiratory apparatus	0	1	0
Chest and hear	3	3	7
Back and spine	1	1	1
Extremities	44	6	21
Sleep	23	1	23
Skin and transpiration	5	3	3
Temperature and generals	10	3	16
Total	260	58	199

(c) Repeated symptoms

For *Plumbum*, we found 24 REPs in 5 provers, for *Piper* we collected 31 REPs in 8 provers (Table 8). With placebo we collected only 4 REPs in 3 provers. As shown in Table 8, the REPs of *Piper* are quite different from those of *Plumbum*, especially the stitching and acute pains, the hurry, restlessness and the irritability, mental confusion and sleepiness. Provers of *Piper* reported headache with a sensation of bursting and heat (congestion and constriction in *Plumbum*). The abdominal, but not gastric, spasms and the itching were similar in the two groups. Both homeopathic medicines had early waking, but in *Piper* it was accompanied by sleepiness in afternoon and evening (two provers), in *Plumbum* by semi-conscious sleep and the waking has a 4 a.m. modality (two provers). REPs of placebo are few and non-specific.

(d) Crossed symptoms

The number of CROs was lower than REPs. For *Piper*, we collected 18 CROs, 2 were collected for

Table 8 Repeated symptoms of *Plumbum*, placebo and *Piper* in comparison: ( ) = volunteer number. ! = not in Kent's Repertory, * = not in Kent's or Synthesis 8.0 Repertory

Repeated of *Plumbum metallicum*	**Repeated of *Piper methysticum***
Skin—Eruption, itching. (21) Male—Excoriation, Scrotum (21!). Mind—Mistakes, writing (24*). Chest—Fullness, Heart (24*). Mind—Activity, desires/Industrious (24!). Mind—Introspection (24!). Extremities—Weakness (24). Head–Congestion (24). Generals—Air, drafts of (24*). Generals—Weariness (24!). Sleep—Waking, early (39!). Mind—Activity desires/Industrious, waking (39*). Stomach—Pain, cramping (45). Mouth–Thick, sensation, Tongue (45*). Mouth—Roughness, Tongue (45*). Mind—Mistakes, writing (45*). Sleep–Semi-Conscious (45*). Sleep—Waking, early (45!). Rectum—Diarrhoea (45). Extremities—Pain, Burning, Forearm and Wrist (48). Female—Pain, stitching, Uterus (48*). Head—Constriction (48). Rectum—Diarrhoea (48). Rectum—Flatus, Diarrhoea, during (48).	Sleep—waking, early (10). Chest—Pain, stitching, left side of chest, aggravated by motion (13). Sleep—Sleepiness, overpowering, with heavy sleep (13). Extremities—Trembling, hand (16). Mind—Hurry (16). Head—Heat of head (16). Mind—Irritability and Anger, loosing control (16). Head—Pain, aggravated looking upward and moving eyes (16). Sleep—Yawning (16). Stomach—Emptiness (16). Abdomen—Pain, cramping (16). Head–Perspiration, occiput (16). Head—Pulsation, temples (16). Head—Pain, bursting (16). Head—Empty, hollow sensation (16). Rectum—Flatus, offensive (16). Mind—Concentration, difficult (16). Extremities—chilliness, upper limbs (16). Extremities—Pain, Knee (16). Mind—Restlessness (Excitement) (16). Mind—Confusion of mind (16). Mind—Sadness (16). Face—Pain, lower jaw (16). Extremities—Pain, lower limbs (16). Mouth—Indented and swollen, tongue (31). Face—Pain, Parotid gland (34). Extremities—Pain, aching, knee, motion (34). Extremities—Swelling, Knee (34). Rectum—Urging (40). Skin—Itching eruption, boils (43). Mind—Confusion, of mind (43).
Repeated of Placebo	
Eyes—Pain, burning (23). Stomach—Pain, burning (23). Skin—Eruption, papular (44). Rectum–Diarrhoea (47).	

Table 9 Crossed symptoms of *Pumbum*, placebo and *Piper*. ( ) = volunteer number, ! = not in Kent's Repertory, * = not in Kent's or Synthesis 8.0 Repertory

Crossed symptoms of *Plumbum metallicum*	**Crossed symptoms of *Piper methysticum***
Mind—Fear, Happen, something will (45, 48)!. Mind—Mistakes, writing: (24, 45)*. Mind—Industrious/Activity, desires (24, 39)!. Vertigo—Rising from sitting: (39, 42)*. Head—Constriction, tension (6, 24, 48). Head—Pain, Sides, left (21, 48). Mouth—cracked, tongue, centre (21, 45)*. External—throat, perspiration (21, 45)*. Stomach—Nausea: (21, 24). Stomach—Pain (21, 45). Abdomen—Distension (39, 48). Abdomen–Rumbling (39, 48). Rectum—Diarrhoea (45, 48). Chest—Constriction, tension (24, 48). Sleep—Waking, 4 a.m. (21, 39). Sleep—Waking, early, too (39, 45). Dreams—teacher, spiritual, of a: (24, 45)*. Dreams—castration, about (24, 48)*. Skin—Itching, scratching, amel. (21, 39). Generals, Food, ice-cream, desire: (6, 39)*. Generals, Pain, burning, externally (45, 48). Generals, Pain, constricting, internally (45, 48)!	Mind—Irritability (16, 19). Mind—Confusion of mind (16, 43). Mind—Concentration, difficult (16, 43). Head—Pain (16, 10). Face—Pain, parotid gland (16, 34). Abdomen—Pain, pressure, amel. (16, 10). Abdomen—Flatulence (10, 40). Rectum—Diarrhoea (16, 40). Rectum, Flatus (16, 40). Stool—Soft (10, 40). Female—Menses, late, too (16, 13). Extremities—Pain, knee (16, 34). Sleep—Sleepiness, overpowering (13, 22). Sleep—Sleepiness, evening (10, 13, 16). Skin—Iching, violent (43, 46). Generals—Heat, flushes of heat (16, 19). Generals—Weakness: (16, 10). Generals—Pain, stitching (10, 13).
	Crossed symptoms of Placebo
	Mind—Dullness (44, 47).Eye—Pain, burning (23, 38)

placebo and 22 for *Plumbum*. 2 CROs of *Plumbum* were dreams (Table 9) and were considered noteworthy in qualitative analysis. Calculating the CROs was difficult because of nuances, for instance constricting and griping pains, stitching and sharp pain.[31]

Statistical analysis

As the SELs and SYMs were not normally distributed (see Methods), we used the Kruskal–Wallis test, and then Dunn's multiple comparison between pairs of groups (Primer biomedical statistical software). The difference of the distribution of SELs and SYMs between *Plumbum* and placebo was significant. The difference between *Piper* and placebo was not statistically significant (Table 10). The nature and incidence of clinical adverse events varied between groups (Table 11).

Discussion

The main criterion for selection of a symptom was that it did not occur in the prover's past history. We gave less importance to Modified/Aggravated symptoms (only 11% in *Plumbum* and much less in *Piper* and placebo). We observed 4 returns of old symptoms (2 in *Piper*, 0 in placebo, 2 in *Plumbum*), which are traditionally included in provings,[32] and the percentage was similar to that of other recent provings.[33] The use of open diaries is demanding and some errors occurred. Nevertheless, the results demonstrate a positive and repeatable pathogenetic action in the *Plumbum* group with qualitative differences between placebo in both verum groups (REPs and CROs return of old symptoms, mental symptoms and chronological distribution of symptoms). The verum groups showed different pathogenetic actions, while in the placebo group, few new symptoms, no hypersensitive volunteers, few CROs, no returned symptoms and no clear picture of a pathogenetic action were found.

The number of concordant symptoms was different in the *Plumbum* and *Piper* groups. This proving confirms a certain reproducibility of homeopathic pathogenesis. However, there are problems including unblinded selection and possible linguistic issues. We plan a further analysis, blind, with bilingual assessors.

Table 10 Statistical analysis (* = $P<0.05$). On the right the number of clinical adverse events (AE), Repeated and Crossed symptoms per group. [ ] = number of SELs/SYMs selected by supervisors in a single prover.

Remedy		SELs (Median) [values of single provers] Kruskal–Wallis test (P = 0.042) *	SYMs (Median) [values of single provers] Kruskal–Wallis test (P = 0.013)*	AE	REP	CRO
Piper	$n = 13$	146 (5) [0-0-0-1-2-4-5-7-7-11-18-18-73]	260 (8) [0-0-0-1-3-5-8-9-11-11-21-32-159]	26	31	18
Placebo	$n = 11$	48 (2) [0-0-0-0-1-2-4-5-11-12-13]	58 (2) [0-0-0-0-1-2-4-7-14-15-15]	21	4	2
Plumbum	$n = 7$	118 (16) (Dunn test *) [3-9-9-16-17-31-33]	199 (29) (Dunn test *) [6-11-21-29-37-47-48]	30	24	22

Table 11 Incidence of adverse events (AEs) in the three groups (a single record = 0.32%, five records = 1.6%)

***Piper*, 5.8–1.6%:** Irritability and heat, Anxiety disorder with autonomic symptoms (restlessness, hurry, trembling, sweat and pulsation in head), Mental confusion, Sadness, Difficult concentration, Bursting headache aggr. from eyes movement, Pain in mouth, Indented tongue, Abdomen spasmodical pain and diarrhoea, Stitching pain in the left chest, Pain and swelling in the knee with loss of movement, Early waking with afternoon drowsiness and heavy sleep; **1.3–1%:** Pain and swelling of parotid gland, Hip pain, Shivering in upper limbs and upper part of the body (except the head), Itching and erythema; **0.6%:** Occipital headache, Face pimples, Dysphonia, Fetid urine, Menstrual retardation, Impaired movement co-ordination, Weariness; **0.3%:** Appetite increased, Stitching pain in stomach, Back pain.

Placebo: 2.9–1.6%: Eyes burning pain, Stomach burning pain; **1.3–1%:** Pharynx-oesophageal troubles (eructation, lump in the throat), Urging and diarrhoea, Maculopapular eruption; **0.6%:** Dullness, Torticollis, Pain in right hypochondria, Uterus contraction, Knee pain, Internal heat; **0.3%:** Indecision, Occiput stitching pain, Pimple in chin, Appetite increased, Nausea and photophobia, Cervical pain, Palpitation, Hip pain, Heat in the knee, Frequent waking.

Plumbum, 5.4–1.6%: Nervous tension and hyperactivity, Mistakes in writing, Constrictive and drawing headache, Cracked, thick and indented tongue, Stomach cramps, Diarrhoea and rumbling, Genital ulcer and excoriation, Stitching pain in uterus, Congestion (hypertension) and constriction with stitching pain in heart region, Burning pain in left forearm, Legs eruptions, Semi-conscious sleep and early waking; **1.3–1%:** Capacity of introspection, Anxiety-alert and trembling, Congestion and constriction in the head, Leg weakness, Itching like pin-pricks, Weariness and prostration, Coldness and sensitivity to drafts of air; **0.6%:** Vertigo, Phosphene, Craving for ice cream, Constipation, Lower limbs trembling; **0.3%:** Conjunctive dryness, Face perspiration, Chapped lips, Gums bleeding, Appetite increased before sleep, Decreased sexual desire.

Placebo

We identified three main, partially overlapping, responses to placebo: a first sub-group, in our experience about 50–60% of the total, with a few symptoms; a second sub-group, about 40–45%, with clear amelioration of the psychological state and/or some physical symptoms; and a third sub-group, about 25–30%, with apparent pathogenetic symptoms. The size of this nocebo group is similar to that described elsewhere.[34,35] Noteworthy is the lower number of mental symptoms in placebo than in verum groups.

Posology

Concerning potency, we found 30C convenient, doses 4–6 times daily provoked sufficient symptoms in a few days. We saw only one adverse reaction in a *Piper* prover who stopped the remedy, while three sensitive subjects (one *Piper* and two *Plumbum*) decreased the intake when they developed strong symptoms, increasing again after the symptoms eased. Symptoms generally disappeared within 2 weeks of stopping medication.

Qualitative parameters of a proving

This proving confirmed the data obtained with a similar methodology with *Arsenicum bromatum:* there were 25–30 REPs and around 15–25 CROs in a group of 8–12 volunteers.[21] From our data, it seems that REPs depend on the degree of hypersensitivity of one or more provers, while CROs are an index of distribution of the symptoms in the different provers. In fact, the ratio REPs/n (n = sample size) was always more than 2 in verum groups and less than 0.5 in placebo, while the ratio CROs/n was 3.1 in *Plumbum*, 1.4 in *Piper*, but only 0.2 in placebo.

Qualitative evaluation of symptoms

Many characteristics of *Plumbum* were confirmed (slowness, melancholy, ennui, burning pains, constrictive and cramp-like pains, trembling and weakness of the limbs), but some symptoms were defined with a new perspective (anxiety, activity, alarm). A peculiar symptom in both *Plumbum* provings was the stitching pain in the chest and between the shoulder blades. With *Piper*, a single prover gave the principal symptoms (hurry, irritability with her sons, pulsating and bursting headache, heat in the head), but other provers gave some REPs: stitching pains in the left side of the chest; an overpowering sleepiness; mental confusion and excitation; unbearable pain and swelling of the knee.

Statistics

We analysed the distribution of SELs and SYMs using the Kruskal–Wallis and Dunn tests. Differences between placebo and *Plumbum* were significant

($P<0.05$). Subjective data such as symptoms are not easily reducible to numbers, but it is possible. The differences between placebo and *Piper* were not significant. We can suggest two explanations: the first is that the result is due to random variation and a larger number of provers is required. The second is that *Piper* and *Plumbum* are very different remedies and while the action of *Piper* is directed mainly to the central nervous system and neuromuscular functions the actions of *Plumbum* are much wider and it is therefore more likely to cause symptoms. The presence of hypersensitive provers only in verum groups, and the relative paucity of symptoms in the placebo group, requires an alternative explanation to random variation.

Conclusions

Hahnemann was convinced that homeopathy and homeopathic pathogeneses (provings) were based on biophysical phenomena[36] and that provings on healthy volunteers reproduce the same symptoms in different trials with different healthy volunteers.[37] Nevertheless, some recent proving trials failed to reproduce specific symptoms. Therefore, either Hahnemann based his therapy on false observations or his experimental methodology was more suitable to see this phenomenon. For this reason we wanted to search a methodology for proving using classical and modern tools. Posology, duration and selection of pathogenetic effects were the main questions.

We chose the repeated administration of a liquid medicine at 30C and to stop the intake only with strong symptoms. We had many symptoms in a few days, which disappeared within 15 days. Pathogenetic symptoms showed a certain repeatability in the same prover and among different provers. The specificity of the symptoms is confirmed by the concordance of our symptoms with the classical German proving. Unusual new symptoms did not arise in verum and placebo in a similar way. The placebo group seems therefore important for the selection of real symptoms.

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Appendix: symptoms concordant with the original proving of Hartlaub and Trinks

The SELs of our proving with identification numbers are given first (prover code-day-hour), K indicates the page of Kent's Repertory. The original symptoms of Hartlaub and Trinks' proving (HT) are given in English, with their number and the initials of the observer. Modalities and associated symptoms in bold

Symptoms of *Piper* present in Hartlaub and Trinks proving of *Plumbum*

1. 19-1p-Afternoon: Hyperthermia < **in the afternoon**.

HT 999: Rising of heat with anxiety in the afternoon (Ng).

2. 10-1p-18.00: Appearance of pyrosis …: the pain was located in a small point, **a stitching pain** in epigastrium, ameliorated by pressure, lasting about half an hour.

HT 336: Stitching from the heart area to the back, often (Ng)

3. 31-6p: On waking, tongue slightly swollen and enlarged: edges indented especially on the left where the edge is **inflamed** and seems to have a little sore; lower surface: three red **pimples**.

HT 182: At 6 in the evening sudden appearance of burning pimples on the tip of the tongue, especially painful when talking, lasting until 10 p.m. (lasted 1 d.) (Ng).

4. 13-1p-09.30: **Stitching pain** in the **left side of the chest**, not modified by respiratory movements.

HT 660: Strong and pressing stitching pain on the left side of the chest, that comes and goes, independent of respiration (Hg).

5. 16-1p-12.30: I always **feel heat** and sweat in my head. **Headache in forehead** and side, aggravated looking upwards.

HT 67: Headache; tearing in the forehead, with feeling of heat in the head and redness without external heat, for 1/8 h., in the afternoon (Ng).

6. 16-2p-13.45: **Offensive flatus** which do not relieve the spasm.

HT 485: Brief slightly noisy winds, of penetrating smell (Hg).

HT 486: Discharges of bad-smelling flatus (Ng).

7. 16-6p-11.00: Sullen, **don't feel like talking**.
HT 18: Don't feel like talking, after lunch (Ng).

8. 40-2p-10.00: **Flatulence** with strong **urge to stool**.
HT 477: Flatulencies urge in vain to discharge, that comes later, with effort, in the afternoon (Ng). Die

Concordant Symptoms of *Plumbum*

1. 6-1p-22.45: After dinner (cheese and beans) I have a slight headache, **like they press (stringere)** my forehead, I wrinkle my forehead.
HT 60: Pressure (**drücken**) in the forehead, more externally (during the second evening). (Ng).

2. 6-5p-24.00: I ate a sandwich: **I was very hungry**; I was not able to speak anymore and **I was sleepy (BEFORE GOING TO SLEEP)**.
HT 255. Feeling of hunger and nausea, the evening before going to sleep (for 6 d.) (Ts.)

3. 21-4:5p-night: Sleep interrupted by repeated awakenings **since 4.00 a.m.** (K,1255a).
39-4p-06.00: I slept badly. **I woke up early** with a feeling of tension, **about 4.30-5.00 a.m.** (for some days).
HT 973. He awakens at 4.00 in the morning (with troubles in the limbs) (Ng).

4. 21-4p-07.00: Appearance of an itchy **excoriation (escoriazione) in the scrotum** area (right) that improves with scratching and cold water (lasted 4 d.) (not in Kent's Repertory but in Synthesis 7.0 and more!).
HT 585. After perspiration, an excoriation **(Wundheit)** of the skin of the scrotum and thigh, if they come in contact. (Hg).

5. 21-5p-11.00: Sudden gastric pain with **massive nausea** that **solves spontaneously after 5 min**.(31/2 h. d. 1° somm.).
HT 271. Nausea and feeling like vomiting (after 2 h.), passing sensation (Ng).

6. 21-6p-05.00: Sudden drawing pain in the **left parietal** region of the head which regressed after a few seconds (K,167a).
HT 49: Slight headache, in the anterior part of the left parietal bone (a. 1 h.). Ng.

7. 24-2p-5:8.00: I feel a certain positive **tension in heart region**. Only **I worry (timore)** that keeping active this emotional tension could exhaust it or exhaust me too much (K,824a).
HT 688. Worry **(aengstlich)**, anxious for the heart. (after 1/2 h.) (Ng)

8. 24-4p-09.30: I would like to rest some more, but I have a certain drive **towards action, to feel engaged** (K,56a, Industrious).
39-4p-06.00: This tension felt as if I had to think: 'ready to go'. It was not a slow awakening, but I felt immediately ready for work. It was a constructive tension, but it was enervating. I felt **more active** than usual, **hyperactive**. My wife instead saw me as less irritable, more calm and less reactive (K,56a).
HT 37: Extremely active, absorbed in the work (knitting), thoughtful. In the afternoon (Ng).

9. 24-3p-19.30: **Weakness in my legs (fiacca alle gambe)** and extremities (K,1231a).
24-3p-23.00: Till one in the morning the feeling of **sluggishness in the legs (fiacca alle gambe)** reminds me of the feeling I often experienced in my adolescence (K,1231a).
HT 831. Weakness in the legs **(Matt in den beinen)** in the afternoon. (Ng)
HT 832. Loss of strength **(Kraftlosigkeit)** in the muscular mass of the legs, while walking (for 1 d.) (Hb).

10. 24-4p-18.00: Immediately after the remedy, I feel a sensation of **weakness in the extremities** as if a **difficulty to exercise** (K,1231b, walking, while).
HT 832. Loss of strength **(Kraftlosigkeit)** in the muscular mass of the legs, while walking (after 1 d.) (Hb).
HT 833. Fatigue **(Müdigkeit)** in the knees ascending stairs (for 1 d.) (Hg).
HT 838: Unusually tired and weak owing to motion. (Hg).

11. 24-4p-11.00: The cephalic tension comes with … a slight sense of congestion, which grips the head, mainly in the **cortical zone** (or **meningeal**) of the cerebral mass; in short in the more external areas (K,128a, inflammation, meninges).
HT 58. Feeling of pressure **(Drücken)** beneath the skull as from blood rushing to the head. (Ts).

12. 24-3p-19.30: Feeling of slight **congestion in the occiput** and the nape of the neck (K,127a).
HT 55. Feeling of heaviness **(Gefühl von schwere)** in the occiput, as it was increased in weight (Ts).

13. 24-5p-**10.00:** I feel sensitive to draft of air (immediately after the remedy).
24-5p-**20.00:** I feel **cold** even if it is not cold at all … I also close the windows to avoid the draught. I then feel that sensation of heat improves **(onset and duration of the symptom)** (K, 1259b, morning continuing … evening).
HT 991. Very cold from the morning till the afternoon (Hg).
HT 993. Feeling of cold, walking in the room (Ng).

14. 24-5p-20.00: Perspiration is oilier **(grassa)** than usual (!).
HT 150: The skin of the face is oily **(fettig)**, bright and greasy, touching it (Hg).

15. 24-1p-24.00: General tension, not disagreeable, but usually I relax more in internally

24-2p-8.00: I have good 'interiorized' energies that are growing from my inner, and the drive of the substance that would seem active to me.

24-2p-16.00: Beyond troubles and moroseness I feel driven by strength to go on without wasting my time in frills.

24-6p-09.00: I didn't take the remedy, because I'm afraid of being unable to work. The weariness is so much.

24-7p-morn: Bad day. Great exhaustion. I do not have energy. No will to take the remedy and to write the journal.

HT 858: The weariness, the weakness, the drowsiness and the pains really oppose themselves to the well-being perceived during the first days, that was exceptionally pleasant. During the first phase the weather was wet and cold, while during the second it was very pleasantly spring (Hg).

16. 39-4p-19.30: I feel like **pin-pricks (punture di spilli)** (K,1329, stinging) all over the body, they disappear then reappear in other areas (!); they are not painful but troublesome like itching.

HT 149: Slight pin-pricks, here and there, in the skin of the face (Hb).

17. 42-1p-14.45: Right after the second remedy intake, a slight bothersome feeling in the mucous membrane of the lower lip (at the edge with the outer lip), almost completely to the left, with a **sour metallic taste** (K,424b).

HT 214: Sour and sulphurous taste deeply in the throat – after a quarter of an hour and after 2 hour and a half (Ng).

18. 42-1p-18.30: Persists the **bothersome feeling in the mucous membrane** of the **lower lip** at the left and the right side with a space of intact mucous membrane. It looks like a little strip of slightly wrinkly mucous membrane, as if it was **chapped** with colour irregularities.

HT 164. –The lips peel daily, without pain, and without perceptible dryness (Hg).

19. 45-1p-11.30: I feel some cramps in the stomach. I crave for dry things, **a sandwich, a biscuit**, also to absorb this abundant salivation (K,484a, 485b, and 486b).

HT 257: All the time a great craving for bread, biscuit, soon after meal, late evening and early morning. (Hg).

20. 45-1p-20.30: The cramping stomach pain persists. It is like a hand **pressing and griping (che stringe)**, strongly (K, 517b).

HT 320: Pressure in the stomach after dinner (Hg).

HT 326. Feeling of contraction in the stomach (after 6 h.) (Ng).

21. 45-6p-23.00: I feel an impatience in my legs, I cannot stay on my seat, it is as if a subtle but **troublesome trembling** went along the whole limb, proceeding from the hip and increasing **from the knee downward** (K,1213b, 1214a).

HT 904: Movements like trembling in the leg (after 2 1/2 h.)(Ng).

22. 45-8p-23.00: I suddenly had **diarrhoea** (K, 609b), at first like rice water and then **watery** (K,643a).

HT 527: Urging to stool, with watery stool (Ng).

23. 45-9p-10.30: Another diarrhoea attack. This time it was **burning as if I defecated fire** (K,626a); this burning pain has remained till now, I feel it stronger on the left; and I also feel abdominal pains. My mouth is full of saliva.

HT 483: Discharges of hot flatulence, that burn like fire (Ng).

HT: 545: Anal burning during stool

24. (K,828a). 48-2p-09.30: Slight sensation of constriction in the chest **(region of the heart)**.

HT 686. Contractions in the region of the heart (after 1/2 h.) (Ng)

25. 48-2p-09.30: Slight sensation of constriction in the chest (region of the heart) with stitching pain in front and **between the left shoulder-blade and the rachis** (K, 938b). This sensation has come even later, inconstantly.

HT 663: Stitching pains in the left pectoral muscle, extending to shoulder blade (Ng).

HT 668: Several strong stabbing pains under right breast extending to shoulder blade (after 1 1/2 h.) (Ng).

26. 48-2p-09.30: Feeling of **burning pain** in the left arm, **from wrist** to the bend of the elbow. (This sensation has come even later, inconstantly) (K, 1092a, 1093a).

HT 740: In the inner side of the right wrist, an area of itching and burning, especially after rubbing (Hg).

27. 48-2p-20.00: Appear sharp **stitching pains** in abdomen at regular intervals (K, 591b).

HT 437: Stitching like a needle under the navel, deeply innerside (after 2 h.) (Ng).

28. 48-3p-10.00: Feeling of constriction (left side) starting **from the nape of the neck** and extending to left vertex, eye and zygoma (K, 197a, forward). This sensation goes and comes at regular interval for 2 h.

HT 59: Pressure from Occiput forward to the front, with the feeling as if the eyes were closing, with heaviness (after 1 h.), ameliorating standing (Ng).

29. 48-8p-10.00: Feeling of heaviness in the head and **state of anxiety (heat** and trembling in all the

body) (these symptoms lasted all day until 9.00 p.m.).

HT 999: Rising of heat and anxiety with sweat, in the afternoon. (Ng);

HT 687: A sharp pain in the region of the Heart, then anxiety with heat and perspiration in the face, that pass quickly (Ng).

30. 48-11p-16.00: **Diarrhoeic** stool and **rumbling** (K,600).

HT 528: Diarrhoea with rumbling (in the belly, without pains (after 2 h.) (Bthm).

References

1 Dantas F. How can we get more reliable information from homeopathic pathogenetic trials? A critique of 'provings'. *Br Hom J* 1996; **85**: 230–236.
2 Hahnemann S. Essay on a new principle for ascertaining the curative powers of drugs, and some examinations of the previous principles. *Hufeland's Journal* 1796; **2**: 391.
3 Sherr J. *Dynamis School. Dynamic Provings*, Vol 1. Malvern: Dynamis Books, 1997.
4 Comissao de Pesquisa—AMHB, *et al.* Bothrops Jararacussu, *Rev Hom*, 1999; **3**: 47–74.
5 Sankaran R. *Provings*. Mumbai: Homeopathic Medical Publishers, 1998.
6 Hahnemann S. (Italian translation of the sixth German edition) *Organon dell'arte del guarire*. Como: Edizioni di red. 1985, parr. 105–145.
7 Hahnemann S. (Italian translation of the sixth German edition) *Organon dell'arte del guarire*, Como: Edizioni di red. 1985, parr. 129, 132.
8 Kent, JT. traslated in Italian from English original edition) *Lezioni di Filosofia Omeopatica*. Como: Lesson XXVIII, La Sperimentazione: Edizioni di red., 1986.
9 Walach H, *et al.* The effect of homeopathic Belladonna 30 CH in healthy volunteers—a randomized, double-blind experiment. *J. psychosomat Res* 2001; **50**: 155–160.
10 Sherr J. *The Dynamics and Methodology of Homeopathic Proving*. Malvern: Dynamis Books, 1994.
11 Dantas F, Fisher P. A systematic review of homeopathic pathogenetic trials ('provings') published in the United Kingdom from 1945 to 1995. in: Ernst E, Hahn EG editors. *Homeopathy——A critical appraisal*. Oxford: Butterworth Heinemann, 1998.
12 Vickers AJ, van Haselen R, Heger M. Can homeopathically prepared mercury cause symptoms in healthy volunteers? A randomized, double-blind placebo-controlled trial. *J Altern Comp Med* 2001; **7**: 123–125.
13 Brien S, Lewith G, Bryant T. Ultramolecular homeopathy has no observable clinical effects. A randomized, double-blind, placebo-controlled proving trial of Belladonna 30C. *Br J Clin Pharmacol* 2003; **56**: 562–568.
14 Elia V, Niccoli M. Thermodynamics of extremely diluted aqueous solutions. *Ann N Y Acad Sci* 1999; **879**: 241–248.
15 Elia V, Niccoli M. New physico-chemical properties of water induced by mechanical treatments. A calorimetric study at 25°C. *J Therm Anal Cal* 2000; **61**: 527–537.
16 Elia V, Niccoli M. New physico-chemical properties of extremely Diluted Aqueous Solutions. *J Therm Anal Cal* 2004; **75**: 815–836.
17 Elia V, Niccoli M. Permanent physico-chemical properties of extremely diluted aqueous solutions of homeopathic medicines. *Homeopathy* 2004; **93**: 144–150.
18 Betti L, Lazzarato L, Trebbi G, Brizzi M, Calzoni GL, Borghini F, Nani D. Effects of homeopathic arsenic on tobacco plant resistance to tobacco mosaic virus. Theoretical suggestions about system variability, based on a large experimental data set. *Homeopathy* 2003; **92**: 195–202.
19 Brizzi M, Nani D, Peruzzi M, Betti L. Statistical analysis of the effect of high dilutions of arsenic in a large dataset from a wheat germination model. *Br Hom J* 2000; **89**: 63–67.
20 Brack A, Strube J, Stolz P, Decker H. Effects of ultrahigh dilutions of 3,5-dichlorophenolon on the luminescence of bacterium *Vibrio fischeri*. *Biochim Biophys Acta* 2003; **1621**: 253–260.
21 Signorini A, *et al. Arsenicum bromatum*: un proving medicinale omeopatico triennale (*Arsenicum bromatum*: a three-years homeopathic drug proving). *Atti del 2° Congresso Nazionale FIAMO* 6–8 Ottobre 2000: 65–70.
22 Allen T. *Handbook of Materia Medica and Homeopathic Therapeutics*, 1889. Reprint Edition: New Delhi: B. Jain Publisher Pvt. Ltd., 1994.
23 Kent JT. *Lectures on Homeopathic Materia Medica.* Reprint Edition: New Delhi: B. Jain Publisher Pvt. Ltd., 1990.
24 Hartlaub, CGC, Trinks, CF. *Reine Arzneimittellehre*, Erster Band. F.A. Brockhaus, Leipzig: available at: Documentation & Library, DHU—Deutsche Homöopathie—Union GmbH & Co KG, Ottostr. 24, 76227 Karlsrhue, Germany, Email: susanne.rehm@dhu.de.
25 Harrison's 15th Edition *Principles of Internal Medicine*, New York: McGraw-Hill, 2001.
26 Signorini A., Il Proving Medicinale Omeopatico nelle Scuole di Omeopatia (Homeopathic drug proving in the homeopathic schools). *Atti del 1° Congresso Nazionale FIAMO*, Roma 2–3 Ottobre 1999, pp. 5-10.
27 Signorini A. La scheda Raccolta Dati e Metodologia di un Proving Omeopatico—Una proposta pratica per le scuole (The data collection form and methodology of a homeopathic proving). *Il Med Omeopata* 1999; **10**: 33–35.
28 Kent JT (Reprint Edition of sixth American Edition). *Repertory of the Homeopathic Materia Medica* New Delhi: B. Jain Publishers Pvt. Ltd., 1990.
29 Synthesis 8.0 (2002-2003)—RADAR Homeopathic Software for Windows. See: www.archibel.com.
30 Glantz S. *Statistica per Discipline Biomediche (original title: Primer of Biostatistics)*. Milano: McGraw-Hill, 1997.
31 The data in Italian are available from asignorini@tiscali.it.
32 Hahnemann S. (Italian translation of the sixth German edition) *Organon dell'arte del guarire* Como: Edizioni di red., 1985, parr. 138.
33 Escola Paulista de Homeopatia. Lapis lazuli, a proving. *Hom Links* 2004; **17**(1):44–47.
34 Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. *JAMA* 2002; **287**(5): 622–627.
35 Staats PS, Staats A, Hekmat H. The additive impact of anxiety and a placebo on pain. *Pain Med* 2001; **2**(4): 267–279.
36 Hahnemann S. (Italian translation of the sixth German edition) *Organon dell'arte del guarire* Como: Edizioni di red., 1985, parr. 11-note, parr. 31-note.
37 Hahnemann S. (Italian translation of the sixth German edition). *Organon dell'arte del guarire* Como: Edizioni di red., 1985, parr. 135.