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Growth Stimulation of Dwarf Peas (*Pisum sativum* L.) through Homeopathic Potencies of Plant Growth Substances

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Key Words
Homeopathy · Anthroposophy · Plant growth regulators · Gibberellic acid

Summary
Background: Efficacy of higher homeopathic potencies is controversial. Universally accepted specific detection assays for homeopathic dilutions do not exist. Basic research has to develop a spectrum of standardized tools to investigate the mode of action and nature of homeopathic potencies. **Objective:** Can the shoot growth reaction of dwarf peas (gibberellin-deficient mutants) be regarded as evidence of treatment with homeopathic potencies of plant growth substances? **Materials and Methods:** Pea seed (*Pisum sativum* L. cv. Früher Zwerg) is immersed for 24 hours in homeopathic potency or control solutions for soaking. Plants germinate and grow in a standard cultivation substrate under controlled environmental conditions. Shoot length is measured 14 days after planting. **Results:** A screening of homeopathic potencies (12x–30x) of four different plant growth substances revealed biological activity of certain potency levels of gibberellin and kinetin ($p < 0.05$). Growth stimulation through gibberellin 17x (5×10^{-18} *M*) was assessed in six independent replications; results confirmed those of the screening ($p < 0.05$). The effect of gibberellin 17x seemed to weaken during the course of the experiments. **Conclusion:** The results back the hypothesis that homeopathic potencies of plant growth substances affect pea shoot growth. Dwarf peas might thus be an interesting system model for studying the action of homeopathic potencies. Further work is required to identify all boundary conditions modulating the reactivity of this system.

Schlüsselwörter
Homöopathie · Anthroposophie · Pflanzenwuchsstoffe · Gibberellin

Zusammenfassung
Hintergrund: Die Wirksamkeit höherer homöopathischer Potenzen ist umstritten. Zurzeit sind keine allgemein akzeptierten spezifischen Nachweisverfahren für homöopathische Verdünnungen bekannt. Aufgabe der Grundlagenforschung ist es, ein Spektrum standardisierter Untersuchungsmethoden zum Studium von Wirkungsart und Natur der homöopathischen Potenzen zu entwickeln. **Fragestellung:** Kann die Reaktion von Zwergerbsen (Gibberellin-Mangelmutanten) zum Nachweis einer Behandlung mit potenzierten Pflanzenwuchsstoffen herangezogen werden? **Material und Methoden:** Erbsen (*Pisum sativum* L. cv. Früher Zwerg) werden für 24 Stunden zur Quellung in die zu untersuchenden Lösungen eingelegt. Die Pflanzen keimen und wachsen in einem standardisierten Substrat unter kontrollierten Umweltbedingungen. 14 Tage nach dem Auspflanzen wird die Sprosslänge gemessen. **Ergebnisse:** Ein Screening von homöopathischen Potenzen (D12–D30) von vier verschiedenen Pflanzenwuchsstoffen ergab eine Wirkung von bestimmten Potenzstufen von Gibberellin und Kinetin ($p < 0,05$). Die beobachtete Wachstumsförderung durch Gibberellin D17 (5×10^{-18} *M*) wurde in sechs unabhängigen Experimenten wiederholt untersucht; die Resultate entsprechen denjenigen des Screenings ($p < 0,05$). Die Wirkung von Gibberellin D17 scheint sich aber im Laufe der Experimente abzuschwächen. **Schlussfolgerungen:** Die Resultate unterstützen die Hypothese einer Wirksamkeit von homöopathisch potenzierten Pflanzenwuchsstoffen auf das Sprosswachstum von Erbsen. Zwergerbsen könnten damit ein interessantes Modellsystem darstellen, um die Wirkung von homöopathischen Potenzen zu untersuchen. Weitere Arbeiten sind aber erforderlich, um die dem System inhärenten Randbedingungen zu identifizieren.

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Introduction

Homeopathy and anthroposophical medicine are well-known methods of complementary health care. Both medical systems include the use of homeopathic dilutions or potencies as a specific therapeutic intervention. The specificity of these remedies is often questioned, however, because of the generally low material concentration of physiologically relevant substances. Though a considerable number of controlled clinical trials exist which show a statistically significant effect of homeopathic potencies compared to placebo, these results are often viewed with skepticism, or their acceptance is postponed until the mode of action can be clarified – as Kleijnen et al. stated: 'We would be ready to accept that homeopathy can be efficacious, if only the mechanism of action were more plausible' [1].

From a point of view which relies on the present state of generally accepted pharmacological knowledge only, it is indeed very difficult to formulate a rationale for a specific action of higher homeopathic dilutions. This problem is especially pronounced when the dilution range exceeds the Avogadro number, i.e. when the probability of finding a single molecule of the mother tincture is virtually zero, as for example at a 30x or even a 30c potency level, corresponding to a dilution of the mother tincture of 10^{-30} or 10^{-60} respectively.

Basic research has tried to establish ways to observe specific effects of homeopathic potencies in preclinical systems. Though hundreds of studies have been published in the last decades [2–12] we do not know of any method which *routinely* allows the measurement of a *characteristic* feature or the determination of a *specific* effect of a higher homeopathic potency. This means that basic research currently has no tool to study either the nature or mode of action of homeopathic potencies. In addition, homeopathic pharmacy has no easy way to gain insight into optimal production procedures as well as storage and transport conditions. We hypothesize that the failure of several clinical studies could be due to inefficient remedies.

Therefore it seems to us of the utmost importance to develop further already existing promising preclinical test systems [13–23], but also to develop new test systems, with special attention to high reliability and moderate expenses in order to facilitate external replication. A broad spectrum of different test systems is needed to answer the question of the specificity of homeopathic remedies – and all subsequent open questions of homeopathic pharmacy.

This paper reports on a new experimental set-up which was designed to overcome common criticisms of earlier work, as summarized in table 1 [12, 24–27]. Methods and first results are described in this publication. All experimental details are given in the section 'Materials and Methods'. The rationale for the experimental design (including controls) is described below. We also tried to perform an adapted and unprejudiced statistical analysis (see section 'Results') and interpretation (see section 'Discussion').

Table 1. Major criticism and problems of preclinical investigations into homeopathic dilutions

No rationale given for experimental set-up
Ethical problems (animal experiments)
Time-consuming set-up, high expenses
Insufficient description of experimental set-up
No blind manipulation and measurement
Inadequate controls
No statistical analysis
No independent replication

The rationale for the set-up chosen was inspired by the interesting results obtained by Bastide and co-workers in their model of bursectomized chicken [17, 18]. In this model chicken embryos were surgically deprived of the Bursa of Fabricius *in ovo* and treated with potencies of bursin (a tripeptide isolated from the Bursa of Fabricius). It was observed that *in ovo* application of high potencies of bursin (15c–20c) restored hormonal response (ACTH, melatonine, corticosterone) to normal levels, i.e. to those of normal chickens not deprived of the Bursa of Fabricius. In short: potencies of an endogenous substance seem to transmit some information which may restore a damaged immune system.

Another example of the use of an endogenous substance (hormone) in preclinical homeopathic potency research is the amphibian metamorphosis model introduced by Endler [28]. It was repeatedly observed that thyroxine 30x slowed down the metamorphosis of frogs (*Rana temporaria*), but in general only where the frog's own internal thyroxine levels were elevated above normal, either due to natural environmental conditions (highland habitats) or due to artificial hyperstimulation [19, 20].

Despite the very interesting results, both experimental models have a common disadvantage: they are quite time-consuming and routinely allow only a few independent parameters to be tested in parallel. We therefore tried to adapt the idea of using endogenous substances as homeopathic remedies to a plant model which in general might be expected to involve less expense. In addition, plants have repeatedly and successfully been used in preclinical investigations of homeopathic potencies [14, 15, 29, 30] since the very beginning of this type of research [31].

Growth stimulation of dwarf peas (*Pisum sativum* L.) through gibberellin GA_3 or GA_1 (specific plant growth substances, sometimes also called plant hormones) is a well-known experiment and a standard textbook example of plant physiology [32]. Most commercial varieties of pea carry the *le* gene leading to dwarf growth. *le* mutants are unable to accomplish the last step of the gibberellin biosynthesis pathway, i.e. they cannot convert GA_{20} into GA_1, the physiologically active form of gibberellin [33]. External application of commercially available GA_3, which is easily converted into GA_1, leads to a striking increase in plant size.

Table 2. Overview of all experiments performed. Experiments 1–17 are in chronological order, experiments 18–21 (series IV) were conducted parallel to the other series

Series	Exp.	n[a]	Main topic	Figure	Table
I	1–7	7	Screening: – 4 plant growth substances 12x–30x	2, 3, 4, 6, 7b	4, 5, 6
			– 3 water control runs	5, 6, 7b	5, 6
II	8–13	6	Main series: – comparison of gibberellin 17x and water		
III	14–17	4	Drift investigation series: – comparison of gibberellin 17x and water	6	5, 6
IV	18–21	4	Substantial doses: – 4 plant growth substances	1, 7a	3

[a]n = Number of independent experiments within a series.

Based on the results discussed above, we raised the hypothesis that dwarf peas might be sensitive to treatment with homeopathic potencies of gibberellin. We thus designed a simple experimental set-up (see section 'Materials and Methods') adapted from standard procedures in plant physiology [32]. Dwarf pea seed were immersed for 24 hours in coded solutions, i.e. gibberellin potencies or corresponding controls (see below). After soaking, 25 peas per parameter were planted into pots with a standard cultivation substrate. After 14 days of growth, each plant's length was measured.

An overview of all experiments performed is given in table 2. In a first series of experiments (screening, series I, table 2), we compared homeopathic potencies of four different plant growth substances: gibberellin (GA_3), abscisic acid (ABA), auxin (IAA), and kinetin. In addition, three blind runs were performed in order to investigate the stability of the experimental system. Based on our working hypothesis we expected that homeopathic potencies of gibberellin ought to influence the plant's growth, whilst potencies of the other three substances ought not to. Furthermore we compared potency series (12x–30x) of the different plant growth substances.

Based on the results of the screening, we decided to perform a second series of experiments (main series, series II, table 2) in order to confirm the results obtained. We thus compared the action of a single potency level of gibberellin to the corresponding water control.

A third series of experiments (drift investigation series, series III, table 2) was performed in order to test the hypothesis of decreased growth stimulation through potentized gibberellin in the course of time. This hypothesis was raised after the evaluation of the main experiments (series II).

In parallel to these three series, we also tested the effect of substantial doses of all four plant growth substances (0.5 m*M* – 0.5 µ*M*). Four experiments were performed with gibberellin and one experiment with abscisic acid, auxin and kinetin (series IV, table 2).

Since there are no established procedures for the preparation of homeopathic potencies of gibberellin and other plant growth substances, we decided to modify existing protocols of plant physiology. 0.5 m*M* gibberellin solutions are recommended for optimal growth stimulation of dwarf peas [32]. We therefore prepared 50 m*M* solutions of plant hormones and defined them as the first potency level (1x). This procedure leads to a comparable number of molecules for all plant growth substances in corresponding potency levels. Correspondingly, the physiologically optimal concentration (0.5 m*M*) is included within the prepared potency series at potency level 3x.

Homeopathic potencies may be prepared according to the multiple-glass method ('H', Hahnemann potencies) or according to the single-glass method ('K', Korsakov potencies). The latter uses one single vessel for an entire potency series (e.g. 3x–30x), whilst the former requires one separate vessel for each potency level (e.g. 28 vessels for a series from 3x–30x). From a scientific point of view, both methods have their own advantages and drawbacks. If the substance potentized has some affinity to the vessel wall due to adsorption, multiple-glass potencies will have concentrations lower than expected from an ideal logarithmic dilution series. Conversely, single-glass potencies will show concentrations higher than expected. In addition, individual vessels might differ in their vessel wall ion release, e.g. because of different effective surface areas due to crizzling. If the multiple-glass method is used, such an effect would introduce physicochemical variations between different potency levels which are due to vessel properties only. This problem does not exist for the single-glass method. For this reason we decided to use the single-glass method for the screening. In later experiments, both types of potentization (single- and multiple-glass method) were used.

In general, two controls were chosen to be used in parallel: i) unsuccussed solvent and ii) succussed, but not potentized solvent. Agitation of fluids in glass vessels induces marked physicochemical changes as increased amounts of suspended and dissolved oxygen and carbon dioxide, and a multitude of ions liberated from the vessel walls [34, 35]. Since these effects are associated with succussion only (and not with dilution), comparison of unsuccussed and succussed solvent yields sufficient information concerning the influence of these purely physicochemical effects on the experimental system. Thus such a 'combined control' yields maximum safeguard against

Table 3. Pea shoot length stimulation through substantial amounts of gibberellin. Data are compiled from 4 independent experiments (experiments 18–21, series IV, table 2). Potencies were prepared with the single-glass method (K-potencies).

Soaking solution	Pea shoot length, raw data, mm			Pea shoot length, relative to the water control, %		
	mean	SD	n	mean	SEM	n
Water control	100.46	27.03	188	100.00	1.90	188
Gibberellin 3x (500 µ*M* GA_3)	372.73	109.58	89	370.56	11.28	89
Gibberellin 4x (50 µ*M* GA_3)	116.51	32.55	92	115.97	3.43	92
Gibberellin 5x (5 µ*M* GA_3)	101.95	25.92	91	101.78	2.74	91
Gibberellin 6x (0.5 µ*M* GA_3)	100.83	25.87	92	100.90	2.71	92

Table 4. General information and global statistics of the experiments of the screening (series I, table 2). Control experiments are printed in italics. p-values were calculated with the F-test (ANOVA). Potency levels 28x–30x of exp. 2 were lost due to technical reasons.

Exp.	Date	Substance	F	p-value
1	*7.10.1998*	*water, 21 identical parameters*	*0.619*	*0.900*
3	*2.6.1999*	*water, 21 identical parameters*	*1.270*	*0.194*
6	*26.10.1999*	*water, 21 identical parameters*	*0.996*	*0.466*
2	28.10.1998	gibberellin 12x–27x, two water controls	1.871	0.019[a]
4	23.6.1999	abscisic acid 12x–30x, two water controls	0.984	0.481
5	21.9.1999	auxin 12x–30x, two water controls	1.243	0.214
7	24.11.1999	kinetin 12x–30x, two water controls	1.724	0.027[a]

[a]Significant values ($p < 0.05$).

an interpretation of physicochemical artefacts as specific homeopathic effects [24]. Potentized solvent was not used as control because of its possible action as a homeopathic remedy [14, 15, 36].

Materials and Methods

Preparation of Homeopathic Potencies and Control Solutions

All potencies and controls used in one experiment were freshly prepared on the day of the experiment (between 7 and 11 am). Potentization medium for potency level 1x was acetone (GR for analysis, Merck, Dietikon, Switzerland), because it is the standard dissolution medium for plant hormones in plant physiology [32]. The potentization medium for all other potency levels (2x–30x) and control solutions was freshly distilled water (Büchi, Fontavapor 250, Flawil, Switzerland) from the same batch and no more than 24 hours old. Potentization vessels were brand-new and rinsed thoroughly three times with deionized water (<0.5 µS/cm, Christ ministil P-24, Christ Aqua Ecolife, Aesch, Switzerland) and twice with distilled water before use. New vessels were used for each independent potency series. Agitation (succussion) was carried out by means of a regular up-down hand movement in the air, i.e. without hitting the vessels against a surface, within an amplitude of about 20 cm. All samples were shaken at a rate of about 2 Hz for 1 min.

Potency Levels 1x–2x

Corresponding amounts of all plant hormones (abscisic acid (±ABA), Fluka, Buchs, Switzerland; gibberellic acid (GA_3), indole-3-acetic acid (IAA), kinetin, the latter all from Sigma, Buchs) were dissolved separately in 1 ml acetone each within sterile 12-ml PP-tubes (Greiner, No. 184 261, Frickenhausen, Germany) and agitated for 1 min in order to obtain a 50 m*M* solution of the corresponding plant hormone (potency level 1x). Potency 2x was prepared by adding 9 ml distilled water to the PP-tube containing potency level 1x and successive shaking.

Single-Glass Method: Preparation of Potency Levels 3x–30x and Corresponding Controls

All control solutions and the potency levels between 3x and 30x were prepared within the same vessel (200 ml glass vessel with twist-off metal cap, No. 9025003 and No. 9030000, Merck). First, unpotentized water (control no. 1) was prepared by filling 100 ml distilled water into the potentization vessel without any further agitation. Immediately afterwards, the content was poured into the corresponding pea immersion dish (see below). Succussed water (control no. 2) was prepared by filling 100 ml distilled water into the potentization vessel and successive agitation. This solution was poured into the appropriate pea immersion dish (see below). In the next step, 10 ml potency 2x (see above) was poured into the vessel, to which 90 ml of distilled water was added. Agitation results in 100 ml of potency level 3x. 89 ml of this solution were discarded. The remaining 11 ml potency 3x served as starting point for potency level 4x. 100 ml distilled water was added to the potentization vessel. After agitation, 100 ml of this solution were discarded. The remaining 11 ml potency 4x served as starting point for the next potency level which was prepared analogously. Potency levels 12x to 30x were not discarded, but poured into the corresponding pea immersion dish (see below). In the experiments with substantial doses of plant growth substances, potency levels 3x–6x were not discarded, but poured into the corresponding pea immersion dishes.

Multiple-Glass Method: Preparation of Potency Levels 3x–30x and Corresponding Controls

All control solutions and the potency levels between 3x and 30x were prepared in different vessels (200 ml glass vessel with twist-off metal cap, No. 9025003 and No. 9030000, Merck). Before use, all vessels were rinsed thoroughly three times with deionized water (<0.5 µS/cm, Christ ministil P-24, Christ Aqua Ecolife) and twice with distilled water. Vessels were not reused, i.e. new vessels were used for each independent potency series. First, unpotentized water (control no. 1) was prepared by filling 100 ml distilled water into a potentization vessel without any further agitation. Immediately afterwards, the content was poured into the corresponding pea immersion dish (see below). Succussed water (control no. 2)

Table 5. Comparison of the two controls (unsuccussed and succussed water): pea shoot length (mm), mean ± standard error, and corresponding p-values for all experiments with these two controls. Experiments 2–7 belong to the screening, exp. 8–11 to the main series, and exp. 16 and 17 to the drift investigation series (see table 2).

Exp.	Series	Unsuccussed water	Succussed water	p-value t-test	p-value U-test
2	I	96.52 ± 6.66	90.83 ± 6.89	0.5569	0.5569
4	I	99.64 ± 4.18	99.96 ± 3.84	0.9552	0.8916
5	I	100.00 ± 4.95	99.80 ± 3.59	0.9741	0.8996
7	I	82.28 ± 5.75	85.04 ± 5.21	0.7255	0.6563
8	II	87.00 ± 4.84	100.32 ± 6.00	0.0915	0.0620
9	II	97.00 ± 4.03	101.04 ± 3.93	0.4764	0.5229
10	II	101.26 ± 3.51	99.05 ± 4.90	0.7181	0.8661
11	II	95.24 ± 6.53	93.41 ± 6.12	0.8423	0.6176
16	III	93.21 ± 5.14	87.05 ± 5.44	0.4153	0.5019
17	III	117.00 ± 3.97	112.84 ± 4.05	0.4673	0.5617

was prepared by pouring 100 ml distilled water into another potentization vessel and successive agitation for 1 min. This solution was poured into the appropriate pea immersion dish (see below). In the next step, 10 ml potency 2x (see above) were poured into another vessel, to which 90 ml of distilled water was added. Agitation for 1 min results in 100 ml of potency level 3x. 11 ml potency 3x and 100 ml distilled water were poured into the next potentization vessel. After agitation, 11 ml potency 4x served as starting point for the next potency level which was prepared analogously. Immediately after production, potency levels 12x to 30x were poured into the corresponding pea immersion dish (see below).

Plant Cultivation

Dwarf pea seed (*Pisum sativum* L., cv. Früher Zwerg) was purchased (ufa Samen, fenaco, Winterthur, Switzerland) and stored in darkness at room temperature. Seed of three different harvests (1997, 1998 and 1999) was used. The first two experiments of the screening (exp. 1–2, table 4) were conducted with 1997 harvest seed. 1998 harvest seed was used in all other experiments of the screening because of the apparent decline in germination rate for 1997 harvest seed. Table 6 gives the list of pea harvest years for the experiments of the main series and the drift investigation series.

At the time of experimentation, any grit and broken seeds were carefully removed. For every cultivation parameter (2 controls and the investigated potency levels) 20 ± 0.2 g of pea seed were weighed out and placed in numbered PP-dishes (125 cm^3, No. 9775, Plastik-Haus, Arlesheim, Switzerland). Potency levels were randomly assigned to the numbers of the PP-dishes. The corresponding code was kept secret so that cultivation parameters (potency levels and controls) were unknown during plant cultivation and measurement. 100 ml of potency or control solution was poured into the corresponding pea immersion dish. Peas were immersed in the solutions for 24 h in darkness.

Pea cultivation substrate was prepared by a 1:1 mixture (v/v) of TKS1 (peat, Floragard GmbH, Oldenburg, Germany), passed through a sieve of 1 cm mesh size, and Vermex F (expanded vermiculite, Vermica AG, Bözen, Switzerland). 450 cm^3 of this mixture was placed in one PP-pot (height 9 cm; diameter at the top 12 cm, at the bottom 8 cm; from Migros, Reinach, Switzerland). Five pots were put together in a PP-tray (length 60 cm, width 15 cm, height 3 cm; from Migros). Every tray was filled with 1000 ml tap water in order to humidify the cultivation medium.

After 24 h of immersion, peas were rinsed with tap water. 25 well-swollen grains were selected from each dish and planted into the 5 pots of one tray (5 grains per pot) at a depth of about 3 cm. All trays used in an experiment were arranged side by side in the center of a large table (405 × 70 cm). At both ends, 2 × 3 trays were prepared analogously, with peas immersed in distilled water in order to eliminate any edge effects due to gradients in humidity or other external parameters. The plants of these trays were not measured at the end of the experiment. Additional watering (500 ml tap water per tray) occurred at days 5 and 8 after pea planting.

Plants were grown in artificial lighting of 60 ± 10 µmol/m^2s photosynthetic active radiation (PAR, measured with a LI-1600 Steady State Porometer with a LI–COR quantum sensor, from LI–COR, Inc., Lincoln, NE 68504, USA) in a 14h:10h light/dark cycle. Temperature (24 ± 2 °C) was controlled by an air conditioning system (National, CS–160YC385E).

Two weeks after the start of an experiment, peas had an average length of about 10 cm. At this stage all plants were cut at the surface level of the cultivation substrate. The length of all plants was measured by stretching them carefully on a sheet of millimeter graph paper. The upper end of a plant was defined as the end of the uppermost leaf; any longer tendrils were disregarded.

After harvest and measurement, all plants and culture substrate were composted. Pots and trays were cleaned by hand with a brush and hot tap water. Both pots and trays were reused in random assignment in subsequent experiments.

Statistical Analysis

All data analysis was performed with the statistics software 'Statistica 4.1 for Mac' (Statsoft, Inc., Tulsa, OK 74104, USA). If not otherwise stated, p-values refer to analysis of variance F tests. Planned comparisons were evaluated with the LSD test only if the preceding F test was significant ($p < 0.05$). This procedure (protected Fisher's LSD) gives a good safeguard against type I error without being too conservative, i.e. it also gives good security against type II errors [37]. As a complementary statistical analysis, non-parametrical Wilcoxon tests were calculated whenever applicable.

Results

Substantial Doses of Plant Growth Substances

One experiment was conducted in order to observe the impact of substantial amounts of plant growth substances on pea shoot growth (fig. 1). The growth of the control plants treated with aqueous potencies of acetone (3x–6x), which was used to dissolve the plant growth substances, did not show significant differences for the four potency levels ($p = 0.946$). The same holds true for kinetin potencies (3x–6x, $p = 0.145$). In contrast, certain potency levels of gibberellin, abscisic acid and auxin influenced pea shoot growth (3x–6x, $p < 0.0001$ for all three plant growth substances).

0.5 m*M* gibberellin (3x) induced large shoots (about 350% of the control), and also 0.05 m*M* gibberellin (4x) seems to have weakly stimulated growth (+15%). 0.5 m*M* abscisic acid (3x) suppressed germination and growth completely; 0.5 m*M* auxin (3x) induced a growth depression of about 30%. 0.05 m*M* abscisic acid (4x) and 0.05 m*M* auxin (4x) both impeded shoot growth by –15%. The dilution levels of 5 µ*M* (5x) and 0.5 µ*M* (6x) did not reveal major influences of any of the plant growth substances ($p = 0.465$ and $p = 0.418$, respectively).

The effect of substantial doses of gibberellin was assessed in three more independent experiments. Results of these, together with the former already mentioned, are presented in

Table 6. Pea shoot length after treatment with gibberellin 17x or the water control (unsuccussed water in exp. 12–15, pool of unsuccussed and succussed water in all other experiments). Experiment 2 belongs to the screening (series I, see table 2), exp. 8–13 to the main series (II), exp. 14–17 to the drift investigation series (III).

Series	Exp.	Date	Potentization type[a]	Pea harvest, year	Pea shoot length, gibberellin 17x group			Pea shoot length, water control group		
					mean, mm	SEM, mm	n	mean, mm	SEM, mm	n
I	2	7.10.1998	K	1997	111.57	5.94	23	93.55	4.77	44
II	8	3.1.2000	K	1998	101.67	4.26	24	93.66	3.94	44
II	9	4.1.2000	H	1998	104.95	6.67	21	99.06	2.80	47
II	10	18.1.2000	K	1998	102.75	4.54	20	100.13	3.01	39
II	11	19.1.2000	H	1998	102.14	5.50	21	94.42	4.47	38
II	12	23.2.2000	H	1997	90.77	3.32	48	87.28	3.84	53
II	13	23.2.2000	H	1998	96.63	3.20	60	94.95	2.42	66
III	14	3.10.2000	K	1997	95.39	4.33	38	91.78	4.19	36
III	15	3.10.2000	K	1999	109.94	3.11	50	112.16	3.35	50
III	16	20.12.2000	K	1998	83.21	4.79	24	90.33	3.72	45
III	17	20.12.2000	K	1999	122.08	3.72	24	114.88	2.82	49

[a]K = Korsakov potencies (single-glass method); H = Hahnemann potencies (multiple-glass method).

table 3. Compared to the water control (pool of succussed and unsuccussed water, see below), analysis of variance ascertains effects of 0.5 m*M* gibberellin (+270%, $p < 0.0001$) and 0.05 m*M* gibberellin (+16%, $p = 0.013$). Lower dilutions (5 µ*M* and 0.5 µ*M*) could not be distinguished from the water control ($p = 0.819$ and $p = 0.955$, respectively).

Screening (Series I): Homeopathic Potencies of Plant Growth Substances and Water Controls (Blind Runs and Succussion Effect)

Three blind runs were performed in order to assess the stability of the experimental set-up, i.e. the experiment was performed with the same number of plants (525 = 25 plants × 21 trays) as in an experiment with homeopathic potencies; however, instead of 21 different parameters (19 potency levels and 2 controls) we used 21 times the same parameter (distilled water). None of these yielded statistically significant differences between the 21 pseudo-parameters (table 4).

The screening included four different plant growth substances. There was no indication that potencies of abscisic acid or auxin exerted any action greater than natural variability on the plant's growth (table 4). In contrast, statistical analysis suggested rejection of the null hypothesis ('no difference between the cultivation parameters') for the potency series of gibberellin and kinetin (table 4). Compared to the water controls, some potency levels seem to have enhanced pea shoot growth (fig. 2).

Succussed and unsuccussed water did not differ significantly for any single experiment of the screening (table 5, exp. 2–7). A two-way analysis of variance of pea shoot length raw data yielded significant differences for the experiment number ($p = 0.007$), but no significant succussion effect ($p = 0.849$), and no significant interaction ($p = 0.879$). Averaging all four experiments, succussed water differed from unsuccussed water by –(0.6 ± 3.9)% (mean ± standard error). As defined a priori, we thus pooled succussed and unsuccussed water into one water control.

Compared to the corresponding pooled water controls (unsuccussed and succussed water), the following potency levels of the gibberellin (GA_3) and kinetin series (fig. 2) show significant differences ($p < 0.05$, LSD test): GA_3 13x (+17.8%, $p = 0.021$), GA_3 15x (+17.0%, $p = 0.033$), GA_3 17x (+19.3%, $p = 0.012$), GA_3 23x (+22.5%, $p = 0.005$), and kinetin 19x (+14.9%, $p = 0.041$).

The gibberellin and kinetin potency curves (fig. 2) show some similarity. In order to test the hypothesis that the two curves do not differ in their shape, we performed a joint analysis of variance of the gibberellin and kinetin potency series with the independent variables experiment number (or potentized substance) and potency level (pooled water control and potency levels 12x–27x) and the dependent variable pea shoot length (normalized to the corresponding experiment mean value). It yielded – as expected – no significant difference between the two series ($p = 0.926$), but a significant effect for the potency levels ($p < 0.001$) and no significant interaction ($p = 0.183$). Thus – according to this analysis – the action of the different potency levels (12x–27x) could not be distinguished for the two series (gibberellin and kinetin).

In order to minimize experimental noise, we pooled both curves (fig. 3). A comparison of the average effects of gibberellin and kinetin potencies with the corresponding average curves of abscisic acid and auxin potencies (experiments 4, 5) and those of the three water control runs (experiments 1, 3, 6) shows a comparable variation for the latter two curves, whilst the gibberellin and kinetin pool exhibits a clearly wider-ranging dynamic behavior (fig. 4).

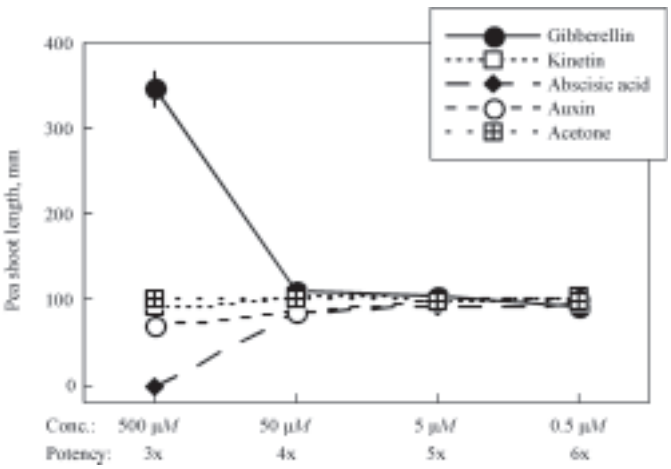

Fig. 1. Effect of a treatment with substantial doses of plant growth substances on the shoot length of peas (mean ± standard error, n = 22–25 plants per parameter, experiment 18, table 2). Potency level and corresponding concentration are given on the x-axis. Standard error is in general smaller than the icons used and therefore not visible.

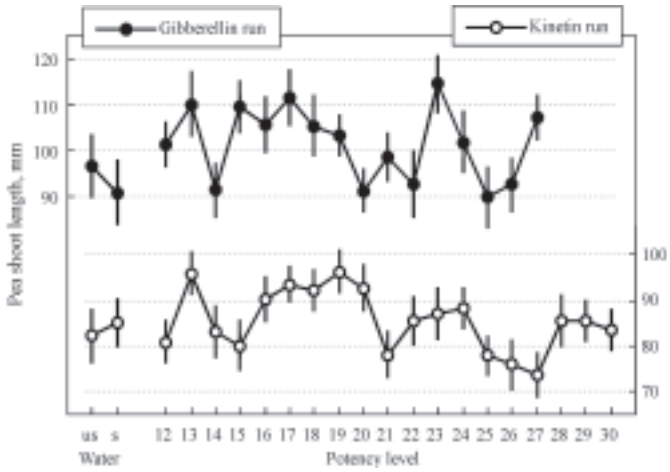

Fig. 2. Length (mean ± standard error) of pea shoots, treated with unsuccussed (us) or succussed (s) water or homeopathic potencies (12x–30x) of gibberellin or kinetin, respectively (exp. 2 and 7 of the screening, tables 2, 4). Potency levels 28x–30x of the gibberellin potency series (exp. 2) were lost due to technical reasons.

Main Series (II), Drift Investigation Series (III), and Pool of All Experiments (I–III): Water Controls (Succussion Effect)

As in the screening, succussed and unsuccussed water did not differ significantly for any experiment of the main series or the drift investigation series (table 5, exp. 8–17 of series II–III). A two-way analysis of variance of pea shoot length raw data yielded significant differences for the experiment number ($p < 0.001$), but no significant treatment effect ($p = 0.861$), and no significant interaction ($p = 0.371$). Averaging all six experiments, succussed water differed from unsuccussed water by + (1.0 ± 3.0)% (mean ± standard error).

Averaging all 10 experiments (of all 3 series, see table 5), succussed water differed from unsuccussed water by + (0.4 ± 2.4)% (mean ± standard error). Correspondingly, analysis of variance of pea shoot length yielded significant differences only for the experiment number ($p < 0.001$), but no significant treatment effect ($p = 0.993$), and no significant interaction ($p = 0.751$). One can thus conclude that the physicochemical alterations induced by the succussion process did not influence pea shoot growth.

Main Series (II): Effect of Gibberellin 17x

According to the results of the screening, the following hypothesis was adopted: 'Treatment with gibberellin 17x induces differences in pea shoot growth relative to the corresponding water control'. Six independent experiments were performed to assess the corresponding null hypothesis (series II, tables 2, 6).

A two-way analysis of variance of pea shoot length raw data yielded significant differences for the main effects treatment ($p = 0.038$) and experiment number ($p = 0.008$), but no significant interaction ($p = 0.944$, fig. 5). On average, the shoot length of peas was increased by + (4.4 ± 2.4)% (mean ± standard error) relative to the plants of the water control. As an alternative statistical analysis, a Wilcoxon Matched Pairs Test was performed for the gibberellin 17x and water treatment means of all six experiments (table 6, series II). This test also yielded significant results ($p = 0.028$).

Drift Investigation Series (III): Effect of Gibberellin 17x

A two-way analysis of variance of pea shoot length was performed on the basis of the four experiments of the drift investigation series (exp. 14–17, table 6, fig. 6). It yielded significant differences for the main effect experiment number ($p < 0.001$), but no significant effect of the treatment ($p = 0.892$) or its interaction ($p = 0.299$). On average, pea shoot length increased by + (0.1 ± 2.7)% (mean ± standard error) relative to the water control plants.

Pool of All Experiments: Effect of Gibberellin 17x

For a final analysis, data of all experiments with gibberellin 17x were pooled (table 6, fig. 6). A two-way analysis of variance of the dependent variable pea shoot length and of the independent variables treatment (gibberellin 17x and water) and experiment number yielded significant differences for both main effects treatment ($p = 0.012$) and experiment number ($p = 0.0001$), but no significant effect for the interaction ($p = 0.337$). Thus analysis of variance comes to the conclusion that the effect of treatment with gibberellin 17x is fairly reproducible and independent of external factors. On average, treatment with gibberellin 17x increased pea shoot length by + (4.6 ± 1.8)% (mean ± standard error) relative to the water control plants.

As an alternative statistical analysis, a Wilcoxon Matched Pairs Test was performed for the gibberellin 17x and water treatment means of all 11 experiments (table 6). This test also yielded significant results ($p = 0.033$).

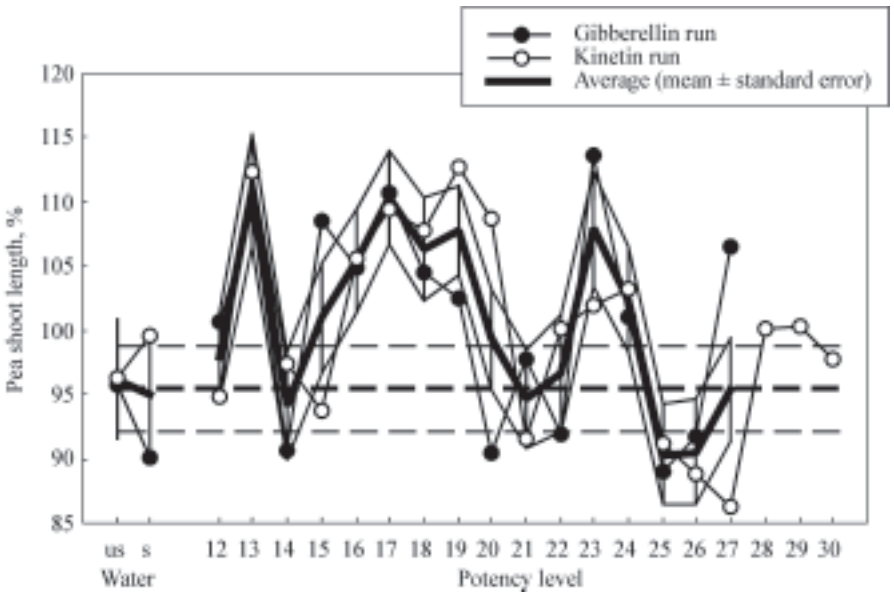

Fig. 3. Pea shoot length (%, relative to the experiment mean) for i) gibberellin potencies (mean only, exp. 2 of the screening), ii) kinetin potencies (mean only, exp. 7 of the screening), and iii) the calculated average of both runs (thick line ± thin lines, mean ± standard error). Horizontal dashed lines represent mean ± standard error for the pooled water controls (us = unsuccussed water; s = succussed water).

Though analysis of variance did not yield a significant interaction between the effect of gibberellin 17x and the experiment number, figure 6 suggests a clear decrease of the relative effect of gibberellin 17x (compared to the water control) in the course of the experiments. A Spearman rank order correlation between experiment number and effect size (%) yielded significant results when including all experiments with gibberellin 17x ($r = -0.636$, $p = 0.035$). Because of the nonparametric nature of this test (rank order), the p-values do not change if the actual date of the experiments (instead of the experiment number) is chosen as the independent variable.

A correlation between age of pea seed and effect size yields no significant results ($p = 0.298$). A correlation between standard error and effect size also gives no significant results ($p = 0.102$).

A three-way analysis of variance of the dependent variable pea shoot length and the independent variables treatment (gibberellin 17x and water), experiment number and potentization type (single- or multiple-glass method) yielded no significant interaction between treatment and potentization type ($p = 0.557$). On average, treatment with single-glass gibberellin 17x increased pea shoot length by + (4.3 ± 2.2)% (mean ± standard error), whilst treatment with multiple-glass gibberellin 17x increased pea shoot length by + (5.0 ± 2.8)% (mean ± standard error) relative to the water control plants.

Comparison of 50 µM Gibberellin (4x) and Gibberellin 17x

The action of substantial doses and homeopathic potencies of gibberellin was compared with respect to the seedlings' length. In order to get a data set with comparable mean effects and comparable number of plants, we compared all four experiments using 50 µ*M* gibberellin (4x, table 3) with the four gibberellin 17x experiments showing the most pronounced effects (exp. 2, 8, 9, 11 in table 6). In this set of experiments, treatment with 50 µ*M* gibberellin (4x) increased shoot length by +16%, whilst gibberellin 17x had an effect of +11%.

The *absolute* effect of 50 µ*M* gibberellin (4x) increased with increasing seedling length (fig. 7a). This means that the *relative* effect was quite constant: for five selected percentiles (10th, 25th, 50th, 75th, 90th) the relative effect was 16 ± 5%.

In contrast, the *absolute* effect of gibberellin 17x was quite constant (fig. 7b). This means that the *relative* effect decreased with increasing seedling length: the decrease was quite smooth for the 5 mentioned percentiles, starting from 25% for the 10th percentile and ending with 6% for the 90th percentile.

Discussion

Water Controls

The results of the three control runs (table 4, fig. 4) back the hypothesis that the experimental system is stable and does not produce false-positive results. Future experiments will include systematic negative controls (control runs alternating with or in parallel to potency experiments) in order to provide definitive evidence for the stability of the chosen experimental set-up.

Pea shoot growth does not seem to be sensitive to the physicochemical alterations induced by the succussion of water within glass vessels, since succussed water did not induce any measurable effect on pea shoot growth, compared to unsuccussed water (table 5). Thus dissolved and suspended air (oxygen, carbon dioxide), glass ion dissolution (Si, B, Na, Mg, Ca, etc.), radical formation through cavitation and other unspecific effects do not influence the chosen experimental system. In addition, any effect of homeopathic potencies (relative to the controls) cannot be due to these unspecific physicochemical

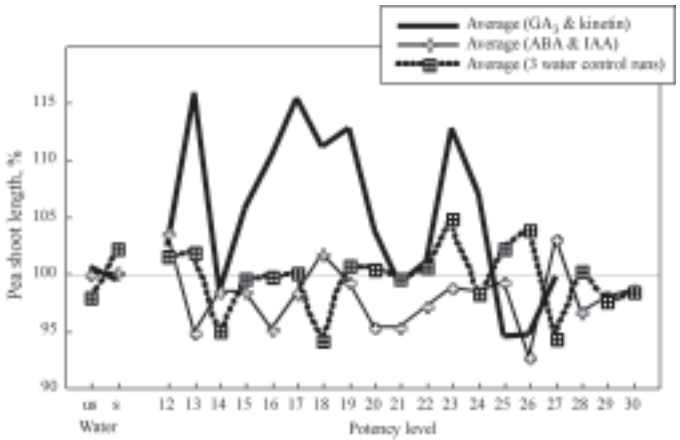

Fig. 4. Pea shoot length (%, relative to the corresponding water control) for the average of i) the gibberellin (GA_3) and kinetin runs (exp. 2, 7), ii) the abscisic acid (ABA) and auxin (IAA) runs (exp. 4, 5), and iii) the 3 water control runs (exp. 1, 3, 6; us = unsuccussed water; s = succussed water). Mean values only; error bars are omitted for clarity. All experiments belong to the screening (series I, table 4).

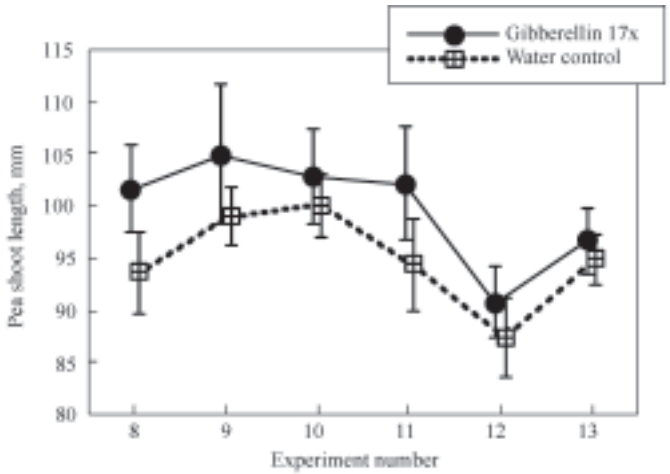

Fig. 5. Shoot length of peas treated with gibberellin 17x or water. Mean values (± standard error) for the 6 independent experiments of the main experimental series II (exp. 8–13, tables 2, 6).

factors, since the succussed water control was analogously prepared as the homeopathic potencies (intensity and duration of succussion, storage length in all used vessels).
As defined a priori, succussed and unsuccussed water were pooled into one water control for all further data analysis.

Screening
With the exception of kinetin, the results of the potency series of the four plant hormones correspond to our expectations: certain potency levels of gibberellin enhanced pea shoot growth (table 4, fig. 2), whilst potencies of abscisic acid and auxin did not exert any effect greater than natural variability (table 4, fig. 4). Contrary to our hypothesis, some potencies of kinetin also enhanced pea shoot growth (table 4, fig. 2).

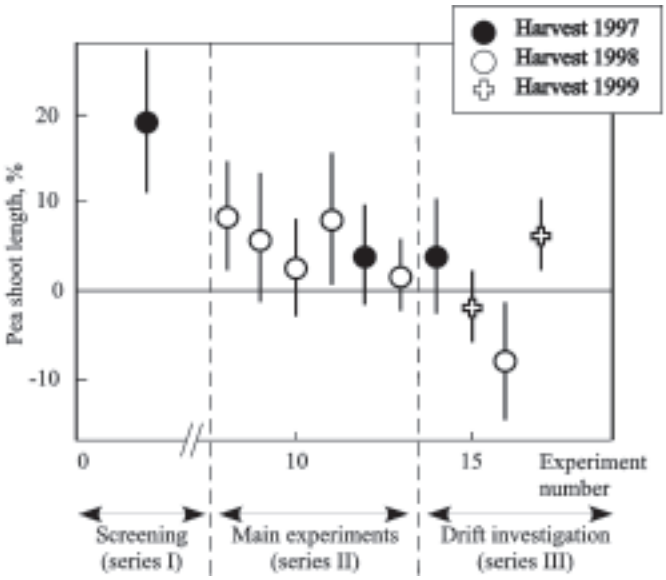

Fig. 6. Effect of treatment with gibberellin 17x on the shoot length of peas (3 different harvests), compared to water (%, mean values ± standard error): overview of all experiments with gibberellin (no. 2, 8–17, table 6).

Chemistry and physiology of gibberellin and kinetin are quite different [38]. In contrast to gibberellin, substantial doses of kinetin do not induce pea shoot growth stimulation (fig. 1). We do not want to speculate much about possible reasons for the similarity of the action of potencies of gibberellin and kinetin. Further investigations and data are needed to clarify this issue. We only wish to point out that there are many classical homeopathic remedies which are similar with respect to one symptom (e.g. sensitivity to heat), but quite different regarding other symptoms. Measurement of only one dimension (or symptom, here: shoot length) thus might yield similar effects of quite different substances.
Interestingly, within both the gibberellin and kinetin series some potency levels seem to be active (e.g. 13x, 16x–19x, 23x), whilst others are not (e.g. 12x, 14x, 21x, 25x, 26x). This phenomenon of active and inactive potency levels has been repeatedly observed by various researchers [15, 22, 29, 39–44]. Since an analysis of variance yielded no significant interaction between potency level and potentized substance (gibberellin or kinetin), we assumed the hypothesis that active and inactive potency levels do not differ for gibberellin and kinetin potencies. We thus dared to construct a common 'curve' of both gibberellin and kinetin potencies (fig. 3, 4). If this assumption is right, the pooled data set should be less distorted through experimental noise. The data of the gibberellin and kinetin pool correspondingly shows much greater shoot length stimulation (+15%/–5%) than the corresponding pool of abscisic acid and auxin potencies or the pooled water control runs (±5%) (fig. 4).
We think that the body of evidence is still too sparse to discuss the question of whether there exists a 'potency level curve'

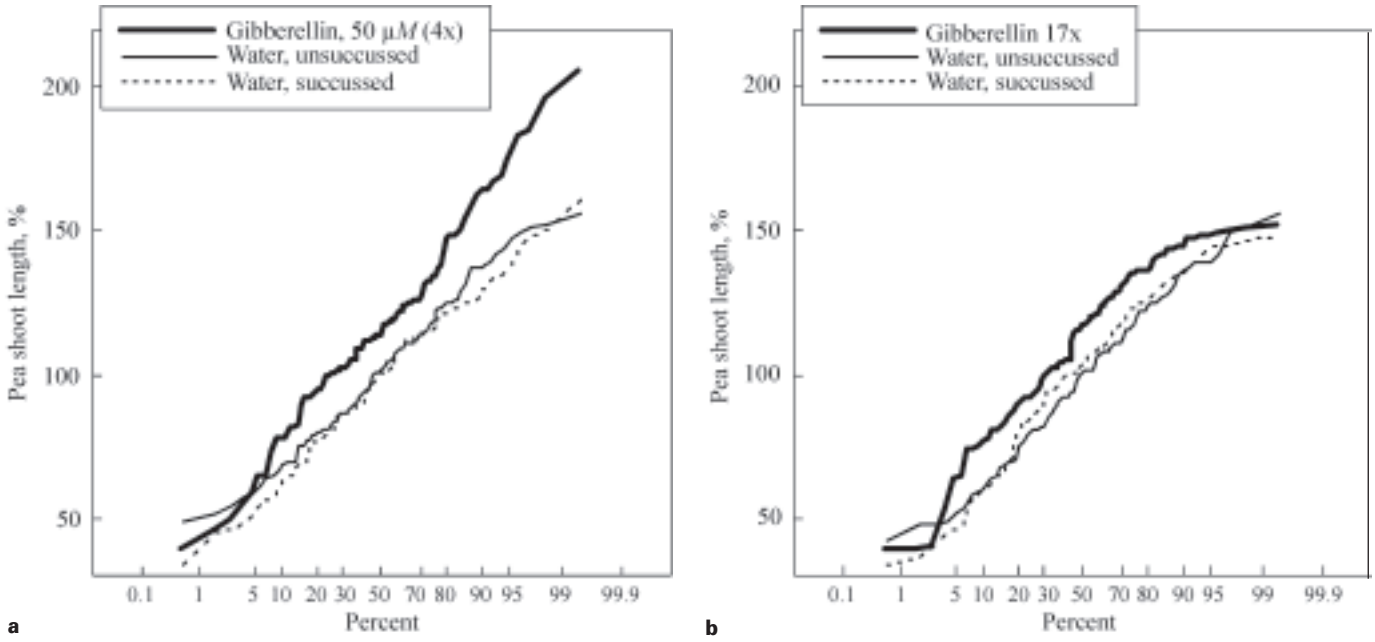

Fig. 7a. Probability plot of pea shoot length (%, relative to the pooled water control; 4 independent experiments, series IV, table 2) treated with either 50 µ*M* gibberellin (4x) or water (unsuccussed or succussed). **b.** Probability plot of pea shoot length (%, relative to the pooled water control; exp. 2, 8, 9, 11, table 6) treated with either gibberellin D17 or water (unsuccussed or succussed). The x-axis is scaled in probability (in normal distribution) and shows the percentage of shoot length whose value is less than the data point.

common to all potentized substances and experimental systems, or whether it varies from system to system and/or from substance to substance.

Main Series

After analysis of the screening, the working hypothesis was refined. We decided to investigate the question of whether gibberellin 17x can be distinguished from pure dilution medium (water) in its action on pea shoot growth. Potency level 17x was chosen because of its position in the center of a broad peak (15x–19x). This feature might make the effect investigated more robust against possible shifts or drifts of the potency curve. Six independent experiments were performed to assess this hypothesis (table 2, 6, series II).

A clear-cut result was obtained: in all six experiments peas treated with gibberellin 17x had longer shoots than the control plants treated with water (fig. 5, $p < 0.05$). However, the effect size (+4.4%) was smaller than expected (+16% according to fig. 2). One may also notice a (not significant) tendency whereby the effect of gibberellin 17x diminished in the course of the experiments (fig. 5). We therefore designed a third series of experiments in order to assess the hypothesis of a decrease in growth stimulation by gibberellin 17x over time, compared to the water control.

Drift Investigation Series

In the drift investigation series (series III, exp. 14–17, tables 2, 6) the effect of gibberellin 17x on pea shoot growth was negligible (+0.1%) and statistically not significant (fig. 6). The effect size was again smaller than in the screening (+16%) or in the main series (+4%). Possible reasons for this decrease are discussed below.

Pool of All Experiments with Gibberellin 17x

A joint statistical analysis of all experiments performed with gibberellin 17x and the corresponding controls gave evidence ($p < 0.05$) for the biological activity of a high dilution of gibberellin (table 6, fig. 6). Since the experiments were randomized and blinded, it is quite improbable that the effects observed are false-positive artefacts, i.e. due to confounders such as inhomogeneities in the cultivation substrate, variations due to soil-seed interactions, the variableness of dwarf gene expression, or the variability of measurement over time. In addition, we can exclude any unspecific physicochemical effects due to succussion (pH alteration, glass ion dissolution, radical formation etc.) as reason for the observed effect of gibberellin 17x, since the potencies were analogously prepared as the succussed water controls and since the latter did not differ from unsuccussed water in their effect onto pea shoot growth.

Gibberellin 17x corresponds to a theoretical dilution of 5×10^{-18} *M*. This is far beyond any pharmacologically relevant concentration (5×10^{-4} *M* – 5×10^{-5} *M*, cf. fig. 1 and table 3). Though one can expect that there are still about 10^6 molecules of gibberellin present in the investigated solutions, the effect observed cannot be designated as a hormetic effect. Hormesis is defined as a positive response of an organism to a substance,

which is given in a 10-fold dose range below NOEL (the no-observe-effect-level, the endpoint of a classical dose-response curve), and which exhibits negative responses at higher concentrations [45]. Thus hormetic responses are restricted to a dose range equivalent to 1 potency level below NOEL, which corresponds to gibberellin 6x (0.6 μ*M*) in our model. In addition we did not observe any effect inversion (from negative to positive) in our experiments. Thus the current concept of hormesis cannot be applied to our results.

The data obtained do not provide an empirical basis for an action of ultra-molecular homeopathic potencies below the Avogadro limit. This question will be the topic of forthcoming investigations, which will also involve systematic negative controls in order to investigate thoroughly the stability of the experimental set-up.

The argument that this growth stimulation is due to cross-contamination during potentization can be ruled out for the experiments using H-potencies, produced with the multiple-glass method: the effect of H-potencies (+5.0%) was comparable to the effect of K-potencies (+4.3%). In addition, the experiments with substantial doses of gibberellin (potencies 3x–6x, prepared with the single-glass method) yielded no evidence for cross-contamination (table 3): the effects of the potency level 5x and 6x were very close to the water control (+1.8% and +0.9%, respectively).

The low homeopathic potency (4x, i.e. substantial gibberellin, 50 μ*M*) seems to increase shoot length by a *multiplicative* law (constant relative effect, fig. 7a). In contrast, gibberellin 17x seems to act by an *additive* law (constant absolute effect, fig. 7b). This points to different modes of action of lower and higher homeopathic potencies of gibberellin. Whilst the substantial dose increased heterogeneity, the gibberellin potency 17x increased homogeneity: small seedlings seem to profit more from treatment with gibberellin 17x. In this sense, the action of gibberellin 17x might be interpreted more in terms of a regulatory effect.

Optically, the stimulatory effect of gibberellin 17x clearly decreased in the course of the experiments (fig. 6). This decrease could not be statistically confirmed by analysis of variance in the sense of a significant interaction between experiment number and treatment. However, a Spearman rank order correlation yielded a significant correlation. We thus come to the conclusion that there is some, but no definite evidence for a decrease of the stimulatory effect of gibberellin 17x in the course of time. We therefore only give a short outline of possible reasons for such a 'decline effect'.

Age of pea seeds does not seem to be the reason for the observed decreasing tendency of the action of gibberellin 17x, since experiments with new seed (harvest 1999, fig. 6) did not yield better results than older pea seed (harvests 1997 and 1998). Since all experiments with gibberellin were performed in winter (table 6), seasonal effects can be excluded as well.

The effectiveness of gibberellin used to prepare the homeopathic potencies was assessed regularly by checking the effect of substantial doses (3x): no decreasing effect could be detected (data not shown).

The number of pea plants used in different experiments essentially remained constant (table 6). Correspondingly, the standard error of the difference between gibberellin 17x and the water control is not correlated with the experiment number. Thus the decrease cannot be due to increased power of the experiments.

Contamination across the experiments could explain the drift observed. Such a contamination would not be due to the potentization vessels since they were brand-new for each experiment and stored in another building. But cross-contamination could be inferred by the pots and trays which were – though cleaned – reused in a randomized fashion, or by the entire laboratory surroundings (table, walls, etc.). If this hypothesis is true, the apparent relative *decrease* of stimulation through gibberellin 17x is in fact due to an *increasing* contamination effect of gibberellin 17x on the water controls. Experiments with brand-new pots and trays, a better cleaning procedure or in another laboratory will help to verify or reject this hypothesis.

Still another hypothesis to explain the decreasing effect arises from clinical experience: it is a well-known phenomenon that repeated application of the same potentized substance at the same potency level may have a much smaller or even reversed effect compared to the effect of the first application. This phenomenon can be interpreted as a learning effect of the organism treated. If a similar phenomenon is responsible for the observed decline effect in homeopathically treated peas, it would be necessary to invoke an entity common to all peas which is able to learn from past experiences. Examples for such an entity are the morphogenetic field as introduced by Sheldrake [46] or the immaterial plant entity as described by Goethe [47] and Steiner [48].

Only experience based on more experimental work will help to verify or reject the discussed hypotheses. We also stress that the evidence for a 'decline effect' is not yet definitive. Further investigations are needed to clarify this issue.

Summarizing, we think that shoot length of dwarf peas might be an interesting system model for investigating the action of homeopathic potencies. Under optimal conditions, the effect size can be as large as 20%, which is visible to the naked eye and quite impressive to observe. However, further work with this system requires deeper knowledge of the boundary conditions restricting effect size, i.e. the reasons for the presumed decline effect.

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