

Position paper

The sting challenge test in Hymenoptera venom allergy

Position paper of the Subcommittee on Insect Venom Allergy of the European Academy of Allergology and Clinical Immunology

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Systemic hypersensitivity reactions to Hymenoptera stings have been reported to occur in 0.8–5% of the general population (1–3). The vast majority of these reactions are due to an IgE-mediated, immediate-type allergy. Symptoms range from mere skin reactions (urticaria, angioedema) and minor cardiovascular or respiratory symptoms to full shock. In a few cases, death or long-lasting morbidity may ensue (3–5). In Europe, most of these reactions result from stings of the honeybee (*Apis mellifera*) or *Vespula* spp. (*V. germanica*, *V. vulgaris*); in Mediterranean countries, *Polistes* spp. (*P. gallicus*, *P. dominulus*) are also of importance. Occasionally, stings by hornets (*Vespa crabro*) or *Dolichovespula* spp., bumblebees (*Bombus* spp.), or carpenter bees (*Xylocobus*) can lead to systemic symptoms (6).

Since the late 1970s, immunotherapy (hyposensitization) with Hymenoptera venoms has been available for treatment of allergic patients. The procedure is highly effective: about 80–100% of those who formerly had reacted systemically do not do so when re-stung after treatment has been initiated (7).

A recent position paper by the Subcommittee on Insect Venom Allergy of the European Academy of Allergology and Clinical Immunology has reviewed in detail immunotherapy with Hymenoptera venoms (6). The classical diagnostic tools in this allergy are history, skin tests, and estimation of allergen-specific IgE serum antibodies. The sting challenge is generally accepted as a method to evaluate the efficacy of immunotherapy. Some authors also recommend it as a diagnostic test in untreated patients (8–12). Provocation tests with Hymenoptera venom preparations injected sub- or intracutaneously are not reliable (13). Moreover, well-tolerated immunotherapy with Hymenoptera venom is not a dependable indication of the tolerance of an actual sting. The sting challenge differs from other provocation tests in that incremental allergen exposure is not possible and insect biology may influence the test result. This paper considers the background of sting challenge tests and aims to give clues to their appropriate performance.

Aims and outcome of sting challenge tests

The principal aim of the sting challenge is to determine the type of reaction to a re-sting in patients with prior systemic symptoms due to a Hymenoptera sting. Sting challenges have been performed in patients

- 1) not treated with immunotherapy, in order to identify those who need this therapy (8, 10, 11, 13–17)
- 2) after the beginning of immunotherapy, in order to evaluate the therapeutic efficacy (13, 18–33)
- 3) after discontinuation of immunotherapy, in order to monitor the persistence of protection (30, 31, 34–38).

The outcome of such challenge tests is shown in Tables 1–3.

One study (14) used sting challenges to assess clinical reactivity in 131 subjects without a history of systemic sting reactions. All subjects had an increased risk of bee stings (beekeepers and their family members), and in some there were indications of immunologic venom sensitization in the skin test or in the RAST. Seven (5.3%) of the subjects without history of previous anaphylactic reaction to a bee sting exhibited a systemic reaction at the challenge.

Furthermore, sting challenge tests allow us to evaluate the prognostic value of diagnostic methods

used in Hymenoptera venom allergy, as well as to assess other factors possibly influencing the outcome of subsequent stings. They also provide an opportunity to study the pathophysiology of anaphylaxis *in vivo* by monitoring related events; e.g., release of histamine, mast-cell tryptase, and catecholamines; complement activation; and consumption of coagulation factors or complement components (12, 39–44).

In larger series (8, 10, 11, 14, 17), sting challenge tests in patients with systemic sting reactions who had not been on immunotherapy have resulted again in systemic symptoms, in the rather low percentage of 28–40%; in two studies with small patient numbers, the reactivity rates were 14% and 58%, respectively (Table 1). Interestingly, when the results of the sting challenges were evaluated for bee or vespid stings separately, higher reaction rates to bee stings (36.5–51.9%) than to vespid stings (9.1–30%) were found (8, 11, 14, 15, 17). Parker (16) performed sting challenges in untreated patients with a history of systemic reaction. Whereas bee-allergic patients developed systemic reactions after the first bee sting, reactions occurred in vespid-allergic patients only if repeated challenges with different vespid species were performed.

A single negative sting challenge test in untreated patients does not seem to be reliable. A second such test performed in 61 vespid venom-allergic subjects who had tolerated a first challenge without clinical response caused systemic reactions in 13 subjects (21%), requiring epinephrine administration in six cases (10). In another similar study in bee-allergic children, 4/30 patients (13.3%) developed severe systemic symptoms only at a second sting challenge (9). Thus, tolerance of a single sting challenge does not definitely indicate absence of hypersensitivity.

When sting challenge tests were performed in patients on immunotherapy, systemic reactions occurred in 0–22.4% (Table 2); a low protection rate of only 47.4% was found in only one study, in which 19 patients were exposed to up to four bee stings (33). Müller et al. (27) also found differences in the efficacy of immunotherapy for bee- and vespid-allergic patients: 5/57 vespid venom-allergic patients (8.8%) developed systemic reactions to a vespid sting in contrast to 34/148 bee venom-allergic patients (23%) stung by a bee. Sting challenge tests in treated patients reassure those who prove to be protected and identify those who need a higher maintenance dose than the usual 100 µg/4 weeks. Such increased maintenance doses have been shown to be effective in most patients in whom protection could not be achieved by standard treatment (45–49).

Sting challenges done in patients off immunother-

Table 1. Sting challenge in untreated patients with history of systemic sting reactions

Authors	Patients	Age (years)	Challenge with		Systemic reactions to sting challenge	
			Bee	Vespid	No	Yes (%)
Hunt et al. 1978 (13)	12		+	+	5	7 (58.3)
Parker et al. 1962 (16)	16	7–55	+	+	9	7 (43.8)
Franken et al. 1994 (10)	228			+	138	90 (39.5)
Blaauw & Smithuis 1985 (8)	86	11–68	38		19	19 (50.0)
				50	38	12 (24.0)
van der Linden et al. 1993 (17)	324	7–72	52		25	27 (51.9)
				272	203	69 (25.4)
Engel et al. 1988 (15)	14	18–61	3		2	1 (33.3)
				11	10	1 (9.1)
Day et al. 1994 (14)	85		85		54	31 (36.5)

Table 2. Sting challenge in patients on immunotherapy

Authors	Patients	Age (years)	Venom for treatment		Treatment duration until sting challenge (months)	Systemic reactions to sting challenge	
			Bee	Vespid (treatment dose)		No	Yes (%)
Yunginger 1979 (33)	19	4–66	19	Ø	After initial treatment	8	11 (57.9)
Golden et al. 1981 (22)	19*		2	(200 µg/4 weeks)		1	1 (50.0)
				18		15	3 (16.7)
				(50 µg/4 weeks)			
Prybylla et al. 1987 (29)	157*	7–68	+	+	6–18	125	32 (20.4)
Hoffman et al. 1981 (24)	25			(100–200 µg/4 weeks)			
Müller et al. 1992 (27)	205	8–71	25	Ø	12	20	5 (20.0)
				(100 µg/4 weeks)			
			148		1–168	130	34 (23.0)
				57	34–121	56	5 (8.8)
				(100–200 µg/4 weeks)			
Gillman et al. 1980 (20)	19*	5–52	18		> 12	14	4 (22.2)
				1	> 12	1	0 (100)
				(100 µg/4 weeks)			
Urbanek et al. 1985 (30)	66	4–20	66	Ø		62	4 (6.1)
				(100 µg)			
Hunt et al. 1978 (13)	18		+	+	After initial treatment	17	1 (5.6)
Goldberg 1994 (21)	19	7–76	19	Ø	> 10	18	1 (5.3)
				(100 µg/3 months)			
Golden et al. 1981 (22)	147		+	+		143	4 (2.7)
				(100 µg/4 weeks)			
Chippes et al. 1980 (19)	42	4–14	+	+	> 15 weeks	41	1 (2.4)
				(100 µg/4 weeks)			
Bäurle & Schwarz 1983 (18)	23		21	2	During course of maintenance treatment	23	0 (0)
				(100 µg/4 weeks)			
van der Zwan et al. 1983 (32)	11	27–56	0	11	> 4 weeks	11	0 (0)
				(100 µg/4 weeks)			
Nataf et al. 1984 (28)	14	15–71	7	7		14	0 (0)
				(100–200 µg/4 weeks)			
Miesbach et al. 1986 (25)	19		0	19	> 2.5 years	19	0 (0)
				(100 µg/4–6 weeks)			
Urbanek et al. 1986 (31)	10	6–20	10	0		10	0 (0)
				(100 µg/4 weeks)			

* Including patients treated with both bee and vespid venom.

apry for 1–3 years produced systemic reactions in 0–17.4% (Table 3). This reaction rate does not exceed that found at challenges performed during treatment. In the individual patient, however, clinical reactivity may recur after discontinuation of immunotherapy, necessitating a new and possibly more prolonged course of immunotherapy.

Risks and adverse effects

Since the aim of the sting challenge test is to identify subjects who develop systemic symptoms, the occurrence of anaphylactic reactions is expected and adequate emergency treatment immediately available. However, this does not preclude the development of severe reactions in some patients. To our knowledge, no fatal reaction has been reported to a sting challenge test. However, in a 14-year-old boy who had previously been treated for bee venom

allergy with a whole-body extract, a diagnostic sting challenge resulted in a nearly fatal reaction; the patient developed severe anaphylactic shock with pulmonary edema, requiring intensive care including assisted ventilation for several days (50).

The development of local toxic or of large local allergic reactions does not cause major problems. A local infection at the sting site has not been observed by us nor has it been reported so far.

Sensitization *de novo* or boosting of already existing sensitization is an important risk of the sting challenge test. It has been shown that after Hymenoptera stings there is an increase in the skin test reactivity and specific serum IgE to the relevant venom (51–54). There are no definite data indicating that as a sequel of a sting challenge test clinical reactivity could also increase. However, it can be assumed that such a mechanism is responsible for some systemic reactions at a second sting challenge

Table 3. Sting challenge after discontinuation of immunotherapy

Authors	Patients	Age (years)	Treatment duration	Treatment discontinued (months)	Venom for treatment		Systemic reactions to sting challenge	
					Bee (treatment dose)	Vespid (treatment dose)	No	Yes (%)
Müller et al. 1991 (38)	86	10–62	32–119 months (mean: 56.4)	10–24 (mean: 13.1)	86 (100 µg/4 weeks)	Ø	71	15 (17.4)
Golden et al. 1989 (35)	74		5–8 years (mean: 6 years)	24		Ø	67	7 (9.5)
Urbanek et al. 1985 (30)	31	4–20	3–4 years	12–24	31 (100 µg/4 weeks)	Ø	29	2 (6.5)
Keating et al. 1991 (37)	51 ^{a,b}		2–10 years (mean: 5.2)	12	15	46	15 44	0 (0) 2 (4.3)
Urbanek et al. 1986 (31)	10	6–20	3–4 years	24	10 (100 µg/4 weeks)	Ø	10	0 (0)
Golden et al. 1989 (34)	29 ^b	Mean: 46.7	5–8 years	12	3 29 (100 µg/4 weeks)		3 29	0 (0) 0 (0)
Haugaard et al. 1991 (36)	25 ^a	Mean: 42.7	36–83 months (mean: 42.8)	12–36 (mean: 25.2)	+ (100 µg/4 weeks)	+	25	0 (0)

^a Including patients treated with several vespid venoms.^b Including patients treated with both bee and vespid venom.

in patients not yet or no longer treated with immunotherapy who had not reacted to a previous challenge (9, 10).

Diagnostic value of sting challenge tests

Challenge testing is a mainstay of allergologic diagnostics, and this holds true also for insect venom allergy. The outcome of such testing depends on the correct selection of an appropriate individual of the culprit Hymenoptera species and on the patient's reactivity, which is determined not only by venom sensitization but probably also by other factors (e.g., interval since the last sting reaction, physical or emotional stress, or inflammatory disease). The rather low reactivity rate of patients not treated by immunotherapy provides strong evidence that immunologic sensitization is a necessary, but not a sufficient, prerequisite for the occurrence of clinical symptoms. The factors possibly interfering with the outcome of re-stings are known only partially; with regard to insect biology, known variables have to be considered when sting challenge tests are performed (see below).

As mentioned above, the reaction rate with the honeybee is considerably higher than with the vespid sting challenge, both in untreated patients and in patients on venom immunotherapy. This may be related to the rather large amount of from 50 µg (55) to even more than 150 µg (56) of venom

delivered by one honeybee sting. It seems that the sting challenge is less reliable with vespids than with honeybees. The venom amount delivered by one vespid sting is much smaller and subject to more variation than that of the honeybee (55). Furthermore, vespids may squirt their venom for defense without actually stinging; e.g., when they are captured for use in a challenge test.

Definite information on the state of reactivity of a patient is obtained only when systemic symptoms occur at the sting challenge test, and even then the patient might not react to a subsequent sting. The failure of the patient to react may indicate absence of sensitization, but it could also be due to other influences than the loss of allergic reactivity. Thus, individual protection obtained by immunotherapy cannot be proven by sting challenge. However, the reaction rates at challenge tests performed in treated patients (Table 2) are obviously lower than those in nontreated subjects (Table 1). This indicates that therapeutic efficacy can be assessed at least in larger patient groups. Of course, an individual patient treated with immunotherapy and not reacting at the sting challenge might still develop symptoms when re-stung. In some investigations (19, 30, 31), repeated sting challenges were performed in patients on immunotherapy who had not reacted to a first sting challenge, and who did not react to further, yearly performed, sting challenges. However, individual patients have also been observed to react not

to a first sting challenge, but to a second one (33). Altogether, sting challenge tests are a useful means to evaluate the state of reactivity in insect venom allergy, provided their outcome is interpreted critically.

Accidental re-stings ("field stings") are of less value in this regard: definite identification of the stinging insect is usually not possible, the venom dose is uncertain, and an objective assessment of the symptoms is often lacking. Indeed, compared with a deliberate challenge test, tolerance of a field sting has been found to be less predictive of the outcome of further stings (38). Reports on the outcome of accidental stings in untreated (57–65) or treated (57, 58, 60, 63, 65–74) patients are summarized in Tables 4 and 5.

Ethical considerations

In a patient with Hymenoptera venom allergy, a sting may induce anaphylaxis, which is potentially life-threatening. Furthermore, an insect sting can sensitize or act as a booster. Thus, the deliberate administration of a Hymenoptera sting has to be weighed carefully.

Immunotherapy is a highly effective means of treating patients with IgE-mediated Hymenoptera venom allergy of the immediate type. In an actively treated patient, the risk of a deliberate sting challenge is smaller than that of an accidental sting, because, in the event of persistent anaphylactic

reactivity, emergency treatment will be available immediately. Furthermore, during sting challenge tests in a large number of patients on immunotherapy, no increase in severity was observed in comparison with the pretreatment reactions (18, 22, 25, 26, 29, 30). On the contrary, most patients were completely protected and only a few still developed – mostly mild – systemic allergic symptoms. Insufficient efficacy of therapy can be identified by the challenge test, and full protection will be achieved in many cases by an increase of the venom dose used for treatment. An argument against a sting challenge test in a treated patient is that a re-sting is not an obligatory event and might even be avoided lifelong. However, if this were so, immunotherapy would also not be necessary. Of course, a well-tolerated sting challenge reassures the patient who is frequently worried profoundly about the possible consequences of a re-sting.

The possibility that a sting challenge test may sensitize or act as a booster cannot be excluded even in treated patients. This has to be considered, particularly when challenge tests are performed after treatment has been discontinued.

Most allergists in Europe and the USA refuse for ethical reasons to perform sting challenge tests in untreated patients with potentially fatal allergy (6, 75). They argue that history and available diagnostic measures, such as skin tests and estimation of venom-specific serum IgE antibodies, are sufficient to decide whether immunotherapy is indicated.

Table 4. Accidental stings in untreated patients with history of systemic sting reaction

Authors	Patients observed/re-stung	Age (years)	Accidental sting		Systemic reactions to sting	
			Bee	Vespid	No	Yes (%)
Lantner & Reisman 1969 (57)	41/18	3–80			7	11 (61.1)
Reisman 1992 (61)	220/220		+	+	96	124 (56.4)
Reisman et al. 1985 (60)	56/28	4–83	+	+	14	14 (50.0)
Przybilla et al. 1992 (59)	248/32	11–70	19	13	19	13 (40.6)
Müller 1990 (3)	29/29		29	Ø	22	7 (24.1)
Valentine et al. 1990 (65)	174/86	2–16	+	+	68	18 (20.9)
Savliwala & Reisman 1987 (62)	28/17	3–67	+	+	15	2 (11.8)
Peppe et al. 1983 (58)	117/117				106	11 (9.4)

Table 5. Accidental stings in patients on immunotherapy

Authors	Patients observed/re-stung	Age (years)	Venom for treatment		Systemic reactions to sting	
			Bee	Vespid (treatment dose)	No	Yes (%)
Thurnheer et al. 1983 (73)	42 ^a /24 ^c	6–70	+	+	17	7 (29.2)
Mokry et al. 1985 (70)	142 ^b /52	Mean: 33	18	(100 µg/4 weeks) 51	37	15 (28.8)
Müller et al. 1979 (71)	31/12	Mean: 33.7	31	(100 µg/4 weeks) 0	9	3 (25)
Peppe et al. 1983 (58)	407/407			(80–200 µg/4 weeks)	351	56 (13.8)
Wyss et al. 1993 (74)	35 ^b /11	Mean: 43	22	18 (100 µg/4 weeks)	10	1 (9.1)
Grant et al. 1981 (68)	17/13		5	8 (100 µg/4 weeks)	12	1 (8.3)
Graft et al. 1987 (67)	94 ^b /49 ^c	4–17	+	+	45	4 (8.2)
Bousquet et al. 1989 (66)	200 ^a /76	4–82	72	128 (200 µg/4 weeks)	71	5 (6.6)
Schuberth et al. 1983 (63)	53/17	3–16	+	+	16	1 (5.9)
Reisman et al. 1985 (60)	127 ^{a,b} /48	7–77	65	84 (50 µg/4 weeks)	47	2 (4.2)
Randolph et al. 1984 (72)	136 ^b /55	7–77	+	+	53	2 (3.6)
Livingston & Reisman 1990 (69)	108 ^b /108	3–72	+	+	105	3 (2.8)
Valentine et al. 1990 (65)	68/36	2–16	+	+	35	1 (2.8)
Lantner & Reisman 1989 (57)	186/37	3–80	+	+	37	0 (0)

^a For patients treated with several vespid venoms, single maintenance dose for each venom is indicated.

^b Including patients treated with both bee and vespid venom.

^c Sting challenges in total number included.

The proponents of the diagnostic sting challenge in untreated patients retort that it is unethical to submit a large proportion of patients with a history of insect sting reactions to an expensive treatment which they do not need. This argument has lost much weight since recent studies (9, 10) have shown that a negative sting challenge in history-positive patients is of limited significance.

Any patient for whom a sting challenge test is intended must be informed fully of the aims and possible risks and consequences of the procedure. Written consent must be obtained and kept on file.

Practical performance of the sting challenge test

Patients

All patients who are to undergo sting challenge must be in good general health and not suffer from any intercurrent, or even mild, flulike disease. Absolute contraindications of a sting challenge include pregnancy, acute inflammatory disease, severe and insufficiently controlled cardiovascular

or respiratory disease, or treatment with drugs which may aggravate systemic anaphylactic reactions, such as beta-blockers. In patients on immunotherapy, the maintenance dose of 100 µg every 4 weeks must have been tolerated without systemic allergic symptoms on repeated occasions and without antihistamine prophylaxis. For heavily exposed persons such as beekeepers and their family members, gardeners, or farmers, an early sting challenge during the first months of immunotherapy will reassure patients about their occupation. For patients who have not been stung by the culprit insect during at least 3–5 years of immunotherapy, a well-tolerated sting challenge may facilitate the decision to stop this treatment. Some authors recommend that immunotherapy not be stopped immediately after the challenge, but be continued for at least 6 months because of the risk of re-sensitization by the sting challenge.

Insects

The sting challenge has to be performed with an insect of the same species that caused the previous

hypersensitivity reaction. Entomologic identification of the insects has to be done carefully by an experienced person. Patients with systemic anaphylactic reactions to stings of bumblebees or *Vespa* spp. are usually treated with the strongly cross-reacting venoms of the honeybee or of *Vespula* spp., respectively, since bumblebee and *Vespa* venoms are not available commercially. Insects of those species whose venom is administered for treatment may also be used for the sting challenge, because sensitization was probably due to the much more common stings of honeybees and *Vespula* spp., respectively.

In honeybees, the composition and the amount of the venom have been shown to depend on the insect's developmental age. Therefore, one uses only insects that have already left the beehive and thus have a mature venom apparatus. Even if this is taken into account, the amount and composition of venom in the venom sac can evidently vary significantly among individual insects (55, 56, 76, 77). *Vespula* spp. may be collected at places where they usually search for food (e.g., bakeries, fruit stands). This will also reduce the risk of misidentification; for instance, *Dolichovespula* spp. may be mistaken for *Vespula* spp., but the former are not scavengers or picnic pests. When collecting insects for the challenge test, one has to be careful not to agitate them, or they may expend their venom by squirting it in defense. Insects may be kept alive at room temperature in the dark for up to 5 days. They are best fed the "bee food" containing honey and sugar used by beekeepers.

Some authors (11, 17, 27) obtain whole vespid nests from local fire departments and cool them to 4°C in the refrigerator. At this temperature, insects survive for up to 4 weeks and can be warmed for provocation tests as needed. This method is very convenient because it avoids the often tedious catching of individual insects. On the other hand, this method offers no means to determine the age of the insect. So far, there are no data available on vespid venom composition in relation to age.

Procedure

The sting challenge must be supervised by an experienced allergist, preferably in an intensive care unit. In any case, complete equipment for resuscitation and a physician trained in using it have to be immediately available from administration of the sting to at least 1 h afterward.

With regard to emergency resuscitation measures, patients have to refrain from drinking, eating, and smoking, starting 6 h before until at least 1 h after the sting challenge. Before the procedure, an intravenous line is installed and left in place also after a

well-tolerated sting for at least 1 h. Pulse rate and blood pressure have to be monitored continuously. Peak flow should be estimated before each sting challenge. If the observed value is below 70% of predicted, the challenge should not be performed.

Before the challenge test, insects may be cooled to 8°C to render them inactive. Cooling reduces aggressiveness and thereby loss of venom. The insect is placed on the extensor aspect of the patient's upper or lower arm and irritated mechanically (e.g., by a forceps) until it stings. To keep the insect in place, it may be put under a small net, beneath a strainer, in a bottomless box, or into a decapitated plastic syringe, the plunger of which is lowered to move the insect to the underlying skin. In either case, one must ensure that the stinger is directed toward the skin surface and that squirting of venom does not occur. The sting event has to be confirmed by close observation, as by the patient's feeling of a characteristic burning pain. In order to ensure delivery of a full sting, insects should be held with their stinger in the skin for at least 60 s. If the stinger remains in the skin, it should be left in place for the same time. Of course, as soon as systemic symptoms occur, the sting event has to be terminated immediately. The development of a wheal-and-flare reaction within minutes after the sting is the only objective indicator of the actual administration of venom; this reaction should be documented quantitatively at a preset time point (e.g., after 15 or 20 min) and with regard to its maximal expression. If no wheal-and-flare reaction develops, the sting procedure should be repeated. It is recommended that vespids used for the challenge test be killed (e.g., by immersing them in concentrated alcohol) and stored deep-frozen to allow reidentification if needed (e.g., in case a patient not reacting to the challenge test develops symptoms after a further sting by an insect presumably of the same species).

After the sting challenge, all patients have to be observed for at least 2 h in the hospital; emergency treatment has to be available during this period. Patients with a history of late-onset anaphylactic reactions (78) have to be followed up long enough to allow any delayed reaction to become apparent.

If a systemic anaphylactic reaction to the sting challenge develops, therapy is initiated according to the rules of emergency treatment (79). All symptoms and all treatment measures have to be documented in relation to the time course of the reaction, and the patient has to be observed until complete resolution of generalized allergic symptoms, including a period to recognize anaphylactic symptoms that might recur, in some cases after a few hours.

The patient has to be informed of the therapeutic consequences of the sting challenge test. In patients

who still develop generalized allergic symptoms, a stepwise increase of the venom maintenance dose to 200 µg is indicated. If the sting challenge test has been tolerated without systemic symptoms, therapeutic success can be largely assumed. However, as already pointed out, a well-tolerated sting challenge does not guarantee complete protection at the next sting. Therefore, the patient should continue to carry an emergency kit (79), but, in the event of a re-sting, this should be used only if systemic symptoms develop.

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