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A DOUBLE-BLIND STUDY OF SYMPTOM PROVOCATION TO DETERMINE FOOD SENSITIVITY

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Abstract *Background.* Some claim that food sensitivities can best be identified by intradermal injection of extracts of the suspected allergens to reproduce the associated symptoms. A different dose of an offending allergen is thought to "neutralize" the reaction.

Methods. To assess the validity of symptom provocation, we performed a double-blind study that was carried out in the offices of seven physicians who were proponents of this technique and experienced in its use. Eighteen patients were tested in 20 sessions (two patients were tested twice) by the same technician, using the same extracts (at the same dilutions with the same saline diluent) as those previously thought to provoke symptoms during unblinded testing. At each session three injections of extract and nine of diluent were given in random sequence. The symptoms evaluated included nasal stuffiness, dry mouth, nausea, fatigue, headache, and feelings of disorientation or depression. No patient had a history of asthma or anaphylaxis.

Results. The responses of the patients to the active and control injections were indistinguishable, as was the incidence of positive responses: 27 percent of the active injections (16 of 60) were judged by the patients to be the active substance, as were 24 percent of the control injections (44 of 180). Neutralizing doses given by some of the physicians to treat the symptoms after a response were equally efficacious whether the injection was of the suspected allergen or saline. The rate of judging injections as active remained relatively constant within the experimental sessions, with no major change in the response rate due to neutralization or habituation.

Conclusions. When the provocation of symptoms to identify food sensitivities is evaluated under double-blind conditions, this type of testing, as well as the treatments based on "neutralizing" such reactions, appears to lack scientific validity. The frequency of positive responses to the injected extracts appears to be the result of suggestion and chance. (N Engl J Med 1990; 323:429-33.)

THE diagnosis of food allergies and other sensitivities by provoking symptoms with injections of extracts of the suggested allergen[1-3] is a procedure so controversial[4] that its efficacy and theoretical basis have been reviewed by the California Medical Association[5] and the American Academy of Allergy.[6] Among the physicians using provocation testing or neutralization treatment are members of the American Academy of Environmental Medicine (formerly the Society for Clinical Ecology) and the Academy of Otolaryngic Allergy. Although a number of studies have been unable to confirm the validity and reproducibility of the symptom-provocation procedure,[7-9] these studies have been criticized by proponents[10,11] because the provocation techniques used did not duplicate those used in clinical practice (even though the technique as practiced differs from office to office). In response to this controversy, we designed and implemented a double-blind study that duplicated the procedures used in clinical practice. Before undertaking the study, we sent the protocol to both advocates and critics of provocation testing and modified it until most agreed that it was a fair and appropriate test of the method. That the protocol was acceptable to the proponents of provocation testing was evidenced by the participation of clinicians who used the method and by financial support from the Academy of Otolaryngic Allergy and the Society for Clinical Ecology.

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METHODS

Protocol

The protocol had four main features. First, it was carried out in the offices of seven experienced clinical ecologists in private practice who were proponents of symptom-provocation testing. Each had at least five years' experience with the technique. Second, only patients in whom symptoms had been consistently provoked during previous unblinded testing were studied. Patients were retested in the same office, by the same technician, who used the same extracts (at the same dilutions with the same diluent) as those found to provoke symptoms during unblinded clinical testing. Third, the study was double-blinded: the technician, the patients, and the investigator or observer had no knowledge of the contents of the syringes. Finally, each patient received a sufficient number of injections that the results for an individual patient could be analyzed for statistical signif-

icance without reference to the results in other patients, to permit the identification of a possible lone "responder."

Patients

All procedures were approved by the University of California, San Francisco, Committee on Human Research, and all patients gave informed consent. Eighteen patients were studied in seven private-practice offices throughout the United States. All patients were between 18 and 60 years of age, had no history of anaphylactic or anaphylactoid reactions, fainting, documented cardiac irregularity, severe laryngeal edema, severe asthma, or epileptic or epileptoid seizures; were recommended for the study by their physician on the basis of previous positive responses to intradermal or subcutaneous injections of "active" substances; and had had no symptoms in response to unblinded injections of the diluent alone. The 18 patients were studied 20 times (2 were studied twice, on different days). Fifteen of the patients were women, and three were men.

On the day of the double-blind testing, the physician had the option of conducting unblinded provocation testing earlier in the day and excluding the patient from the study if he or she did not respond as in previous clinical testing. None of the physicians chose to conduct such unblinded testing, and none withdrew any patient from the study, though the physicians could also have done so on the basis of a patient's self-reported condition on that day.

Procedures

The substances for the active injection, its concentration, and the method of the injection were chosen for each patient by his or her physician on the basis of the patient's previous unblinded clinical tests. These data are presented in Table 1. Of the 20 testing sessions, "underdoses" of the active substance were given in 17, and "overdoses" in 3. These doses were relative to a "neutralizing dose," defined as the dose that when injected in a volume of 0.1 ml, resulted in a wheal of 7 to 8 mm, which enlarged by 2 mm in 10 minutes. Thirteen patients were tested with foods, two with yeast, one with "mold A," and two with ethanol. The injections were given intradermally in 16 testing sessions and subcutaneously in the other 4. The diluent was normal saline, though whether it contained preservative or not depended on the routine practice at each office.

Although routine clinical skin testing normally takes three hours (usually with testing of five or six different substances), we wished to minimize the number of active injections and consequent discomfort. With an observation period of 10 minutes after each injection and several more minutes for recovery after symptom provocation, only four or five injections could be made in an hour. For a conservative limit of 12 injections, we chose to use a protocol with 3 active and 9 control injections. With this protocol, the results for an individual patient could reach statistical significance (with Fisher's exact test) under the following circumstances: perfect identification of all active and placebo injections ($P<0.0045$), one false positive and no false negative results ($P<0.018$), two false positive and no false negative results ($P<0.045$), and no false positive and one false negative result ($P<0.045$).

One of the authors acted as an observer to ensure that the procedures were strictly adhered to; he also recorded the time course and occurrence of the patients' orally reported symptoms. For each test, a tray was prepared with 12 unmarked syringes. Each of the three syringes with active injections was assigned randomly (by a combined die-and-coin toss) to 1 of the 12 positions on the tray. The remaining syringes were filled with diluent. The technician who prepared the syringes placed the code in a sealed envelope, which was given to the observer but not opened until the testing was completed. This technician was the only one who knew the injection sequence. A different technician then used the syringes in order (1 through 12) and alternated the injections between arms; the first side injected was decided by the flip of a coin. The injections were separated by at least 10 minutes. After each injection, the injection site was covered, and the observer recorded any symptoms reported by the patient at 1-minute intervals for 10 minutes. At the end of the 10-minute period the patient had to decide whether the injected substance had been active or control. The symptoms reported by the patients that were associated with an injection presumed to be active included itching of the nose, watering or burning eyes, plugged ears, a feeling of fullness in the ears or ringing ears, a dry mouth, a tight or scratchy throat, an odd taste in the mouth, tiredness, headache, nausea, dizziness, epigastric discomfort, scalp or facial tingling, a feeling of tightness or pres-

Table 1. Responses of 18 Patients Forced to Decide Whether Injections Contained an Active Ingredient or Placebo.

Patient No.*	Sex	Substance	Route†	Dose‡	Neutralizing Dose§	Office No.	Active Injection		Placebo Injection		P Value¶
							Response	No Response	Response	No Response	
3	F	Chocolate	ID	Under	Yes	2	2	1	1	8	0.13
1	F	Wheat	SC	Under	No	1	2	1	2	7	0.24
14a	F	Bakers' yeast	ID	Under	No	5	2	1	2	7	0.24
12	M	Potato	ID	Under	No	5	1	2	0	9	0.25
16	F	Ethanol	ID	Over	No	6	2	1	3	6	0.36
18	F	Ethanol	ID	Under	No	7	2	1	4	5	0.50
14b	F	Brewers' yeast	ID	Under	No	5	1	2	2	7	0.87
4	F	Chocolate	ID	Under	Yes	2	1	2	2	7	0.87
5	F	Wheat	ID	Under	Yes	2	1	2	2	7	0.87
9	F	Apple	ID	Under	No	2	0	3	0	9	—
2a	M	Milk	SC	Under	No	1	0	3	1	8	0.75
13	M	Bakers' yeast	ID	Under	No	5	0	3	1	8	0.75
15	F	Wheat	ID	Under	No	6	1	2	3	6	0.76
6	F	Corn	ID	Under	Yes	2	0	3	2	7	0.55
8	F	Beef	ID	Under	Yes	2	0	3	2	7	0.55
17	F	Mold A	ID	Under	No	7	1	2	5	4	0.50
2b	M	Wheat	SC	Over	No	1	0	3	3	6	0.38
7	F	Orange	ID	Under	Yes	2	0	3	3	6	0.38
10	F	Potato	ID	Under	Yes	3	0	3	3	6	0.38
11	F	Chicken	SC	Over	No	4	0	3	3	6	0.38
Total	—	—	—	—	—	—	16	44	44	136	0.78‖

*Patients were numbered in the order they were studied. The order in the table is related to the degree that the results agree with the hypothesis that patients could distinguish active injections from placebo injections. The results listed below those of Patient 9 do not support this hypothesis: placebo injections were identified as active at a higher rate than were true active injections. The letters "a" and "b" denote the first and second testing sessions, respectively, in Patients 2 and 14.

†ID denotes intradermal, and SC subcutaneous.

‡An underdose was one that was lower than the neutralizing dose, and an overdose one that was higher.

§A dose that, injected in a volume of 0.1 ml, resulted in a wheal of 7 to 8 mm and that enlarged by 2 mm in 10 minutes. Neutralizing doses were given to some patients after they reported symptoms.

¶Calculated according to Fisher's exact test, which assumes that the hypothesized direction of effect is the same as the direction of effect in the data. Therefore, when the effect is opposite to the hypothesis, as it is for the data below those of Patient 9, the P value computed is testing the null hypothesis that the results obtained were due to chance as compared with the possibility that the patients were more likely to judge a placebo injection as active than an active injection.

‖The value is the P value associated with the test of whether the common odds ratio (the odds ratio for all patients) is equal to 1.0. The common odds ratio was equal to 1.13 (computed according to the Mantel–Haenszel test).

sure in the head, disorientation, difficulty breathing, sleepiness, depression, chills, coughing, jaw tightening, nervousness, tension, intestinal gas or rumbling, and aching legs. If the patient reported that the substance was active (i.e., that symptoms had been provoked), then the next injection was delayed for 10 minutes. At the end of that time, the patient indicated whether the symptoms had cleared. If so, testing recommenced; if not, the injection was delayed for another 10 minutes. This process continued until the patient reported that the symptoms had subsided to base line. Some physicians administered an unblinded, predetermined neutralizing dose to patients reporting symptoms. Neutralizing injections were given, after any injection (active or control) judged to be active, to seven patients in two offices (Table 1).

To analyze the data for all patients, we used the Mantel–Haenszel test to compute the common odds ratio.[12] The odds ratio — the odds of the patient's reporting symptoms after an active injection divided by the odds of the patient's reporting symptoms after a control injection — measures the size of the effect. Questions concerning habituation of responses and the effects of neutralization on subsequent injections were addressed by examining the odds of eliciting a symptom on the second and on the third active injection.

Results

Table 1 shows the patients' responses as well as the probability of obtaining such responses under the null hypothesis (no difference in the numbers of injections judged to be active or control). Across all sessions, the proportion of injections judged to be of the active substance was independent of the contents of the syringes. Twenty-seven percent of the active injections (16 of 60) were judged to be the active substance, as were 24 percent of the control injections (44 of 180). The strongest association in an individual patient (Patient 3) between reports of symptoms and active injections yielded a probability due to chance of 0.13 associated with an odds ratio of 9.4. One would expect results with this probability to occur by chance alone two to three times in 20 test sessions. Thus, none of our patients were unequivocal "responders" on the day of testing. The symptoms that were provoked were generally unrelated to the contents of the syringes. Furthermore, the overall results were quite random. One patient (Patient 9) reported no symptoms after any injection. Nine of the 20 sessions (45 percent) had a greater frequency per injection of reports of symptoms after active injections than after placebo injections (Patients 1, 3, 4, 5, 12, 14, 16, and 18) (Table 1), whereas another 9 sessions (45 percent) had exactly the opposite results (Patients 2, 6, 7, 8, 10, 11, 13, and 17) (Table 1). There were no consistent differences in results according to sex, substance injected, route of injection, or testing location (office), as can be determined from the results shown in Table 1. It is unlikely that the results were influenced by sensations at the injection site, since itching was reported at the site by only three patients (for 1 injection each), and stinging by nine patients (median, 3 injections; range, 1 to 12).

The Mantel–Haenszel test for homogeneity of the odds ratios was not significant ($P = 0.76$, $\chi^2 = 12$, $df = 16$), providing no evidence for an underlying distinction between "responders" and "nonresponders" in the study group. The results were consistent with the data having come from a single population in which the best estimate of the mean population (common) odds ratio is 1.13 (i.e., the odds of reporting symptoms after an active injection are 1.13 times the odds of reporting symptoms after a control injection). With this experimental paradigm, if the population odds ratio were 1.0 (i.e., no effect whatsoever), a sample overall odds ratio as divergent from 1.00 as 1.13 would occur more than 75 percent of the time ($\chi^2 = 0.03$, $df = 1$). Even if the sample odds ratio of 1.13 were the true population odds ratio, this would reflect a tiny effect. If this effect were present in the analysis of data from any individual patient, with three times as many control injections as active injections, one would need 726 active injections and 2178 control injections to have an 80 percent probability of detecting this effect at the 0.05 level of statistical significance. Thus, an effect of this size could have no clinical usefulness.

Among the seven patients who were given neutralizing doses, the rate of false positive results was actually greater than the rate of true positive results. Most of the time, the neutralizing dose was given after symptoms had been "provoked" by a control (diluent) injection. The neutralizing dose was as effective in relieving these symptoms as it was in relieving those occurring after an active injection. In most cases a single neutralizing injection relieved the symptoms, and in no instance were more than two neutralizing doses administered. The injection of a neutralizing dose did not affect the sensitivity of the test procedure; the incidence of symptoms provoked after the neutralizing doses was similar to the overall rate and did not differ between active and control injections: 24 percent for active injections (4 of 17) and 23 percent for control injections (12 of 53).

The provocation of symptoms by either a control or an active injection did not significantly change the likelihood of patients' reporting symptoms after subsequent control or active injections. Thirty percent of the patients (6 of 20) accurately identified the first active injection, whereas 25 percent (5 of 20) accurately identified the first control injection. The accuracy of the identification of subsequent active injections was comparable: 30 percent (6 of 20) for the second active injection and 20 percent (4 of 20) for the third active injection. None of the differences were statistically significant. We thus conclude that the results did not reflect changes in sensitivity due to neutralization, habituation, or otherwise undefined "symptom fatigue."

Differences in the routes of injection — subcutaneous or intradermal — had no apparent effect on the rate of the occurrence of symptoms, though only a large effect could have been detected, since only three patients received subcutaneous injections. Similarly, there were no differences in the rate of occurrence of symptoms after an overdose or underdose of the active substance. Despite concern that an overdose might be

detected by the patients, such injections were not associated with the occurrence of symptoms any more frequently than were control injections.

All seven of the participating offices were equally unsuccessful in providing a patient whose symptoms were reliably correlated with the syringe contents under double-blind conditions. We thus have no reason to suspect that differences in technique between offices somehow affected our results.

In looking for more subtle effects of the injections, we wondered whether the duration of symptoms provoked by active injections differed from that of control injections. Since the patients' symptoms were recorded minute by minute, we computed the number of minutes that symptoms persisted after the two types of injection. There was no significant difference in the duration of symptoms after active as compared with control injections. Reported symptoms lasted a mean (±SD) of 1.9±2.1 minutes after active injections and 1.5±1.3 minutes after control injections ($P>0.15$). We did not observe any major differences in the magnitude of reported symptoms, but we did not study this systematically.

Discussion

Some have claimed that food allergies can best be identified by the so-called provocation–neutralization method, which "consists in the production of symptoms by giving an intracutaneous injection of a provoking dose of the food extract, then relieving these symptoms by giving successive intracutaneous injections of other dilutions of the same food extract, until the neutralizing dose is found."[13] The symptoms produced include headache, a feeling of nasal stuffiness, malaise, depression, fatigue, yawning, gas, discomfort, bloating, belching, feelings of anger, memory loss, a feeling of submissiveness, and tightness in the chest.[14] Kailin and Collier have reported that neutralizing injections relieved such symptoms more than 70 percent of the time; however, control (diluent) injections produced a similar rate of relief.[15] Our study was designed to duplicate the provocation-testing procedures used in clinical practice, as a further test of this method of diagnosis. We certainly did not expect the results that we obtained in these studies, since we had observed unblinded clinical testing in which active injections seemed to provoke symptoms readily. In our study, the active injections did provoke symptoms, but at a surprisingly low rate (27 percent), whereas the control (diluent) injections provoked symptoms at a surprisingly high rate (24 percent).

We had expected the rate of reaction to the diluent to be much lower, since previous testing was a requirement of entry into the study. However, the diluent injection had been tested without blinding only once or twice in each patient, and thus we have no good measure of the control reaction rate. We do not believe that the symptoms were provoked by something in the saline diluent, for the following reasons. First, only 25 to 30 percent of the injections provoked symptoms. Second, the patients did not respond to the diluent injection in the unblinded testing. Third, the patients' symptoms were relieved by the neutralizing dose, which contained a concentration of diluent identical to that of the provoking injection. If the biologic effects are related to the concentration of some hypothesized contaminant in the injections, then the concentration that provokes symptoms cannot be the same as the one that neutralizes them. Willoughby[16] has indicated that a dose that provokes symptoms can be considered to neutralize them as well, if the symptoms disappear within 20 minutes; however, he does not describe a single concentration that rapidly provokes and rapidly neutralizes symptoms. Finally, if all the bottles containing diluent contained a substance that would provoke symptoms, it is difficult to imagine a mechanism by which patients, in unblinded testing, could have been found to be sensitive to some "active" agents and not others (which have the same diluent). For these reasons, we conclude that the symptoms provoked by the control and active injections were unrelated to any substance present in all bottles. Rather, we propose a simpler explanation of the results: the symptoms were placebo responses, generated spontaneously. In one review of a number of studies involving a total of 1082 subjects with conditions ranging from headache to postoperative wound pain, the placebo response rate was found to range from 15 to 58 percent, with an average (±SD) of 35±2 percent.[17]

Our study would have been even more powerful if all the patients had been studied on two days (with three active and nine control injections on each day): one day under unblinded conditions and the other under double-blind conditions. In this way the influence of suggestion could have been completely isolated as the independent variable. However, there had been no indication that patients reported symptoms inconsistently. Indeed, we designed the study so that patients were chosen for their consistent selective sensitivity to active injections under unblinded conditions. The physicians had the opportunity to withdraw patients from the study, both after the initial selection and on the day of the testing session. Thus, we must assume that within the range of accuracy of the clinical testing routinely performed in these physicians' offices, the patients were "responders" under unblinded conditions and "nonresponders" under double-blind conditions. We conclude that the technique as practiced works only if practiced unblinded — that is, under the influence of direct or indirect suggestion. This same conclusion can be drawn from a study of symptom-neutralization procedures, in which the rate of symptom relief was independent of the contents of the syringe.[15]

Our study was conducted primarily with provocation doses that were lower than the neutralizing doses. Such "underdoses" were chosen for several reasons. Proponents have asserted that the symptoms provoked by underdoses are stronger, have a more rapid

onset, and are somewhat briefer than the symptoms provoked by overdoses. With underdoses, there is less chance of a local skin reaction that would violate the double-blinding. The finding that underdoses provoke symptoms would establish that the dose–symptom curve is not monotonic (that dilutions both greater and less than the neutralizing dose stimulate more intense symptoms than does the neutralizing dose). A dose–symptom curve with a minimal value at the neutralizing dose would justify treatment with the neutralizing dose, since any other dilution would produce more intense symptoms. On the other hand, if underdoses did not provoke symptoms, then there would be no basis for clinically determining the concentration of the neutralizing dose, since underdoses could be used as treatment doses, without concern for the possibility of provoking adverse symptoms. Our results show that underdoses do not provoke symptoms at a rate greater than that for placebo, and that the symptoms do not last significantly longer than those associated with the placebo responses. Thus, in these patients, symptom provocation due to an underdose is not an adequate justification for claiming that treatment with a neutralizing dose is necessary.

It is regrettable that every patient undergoing challenge or provocation testing is not tested in a double-blind fashion, so that the effect of suggestion or anxiety on the end points could be evaluated. If they were so tested, the problems with the validity of the method that we found would have been discovered decades ago. Double-blind testing is easy to incorporate into the routine use of provocation testing or wheal measurements. Indeed, routine practice in standard allergy testing includes the use of diluent tests because sensitivity varies in various parts of the back, and even such standard tests may not be immune to the influence of psychological factors.[18-20] It should be emphasized that double-blind testing is needed not only in clinical medicine but in the physical sciences as well. Langmuir has reviewed several areas in physics in which nonexistent phenomena were the subject of hundreds of papers.[21] These phenomena and provocation testing share the following characteristics: the magnitude of the effect is substantially independent of the intensity of the cause, the effect is close to the limits of detectability, there are claims of great accuracy (or selectivity), and the results are explained by theories that are contrary to common experience.

If the development of the provocation–neutralization technique was determined primarily by placebo responses, then we would expect differences in technique from office to office without a noticeable difference in the outcomes observed by the physicians. This is certainly the case in the current study. Some physicians believed that the best response would be obtained from those who had had little or no treatment, whereas others believed that the patients who had had more treatment were more likely to respond. Similarly, there was disagreement about whether neutralization during the session would affect the subsequent responses in that patient (neutralization after the occurrence of symptoms had no effect on our results). One would have expected some consensus on this issue before our study began if these were not placebo responses, since neutralizing doses are commonly used to relieve acute symptoms, as well as to provide "protection" against subsequent exposure to the substance.

Healing systems without a sound scientific basis flourish in the vacuum created by the inability of modern allopathic medicine to understand or treat many common symptoms. A system of treatment based on the relief of symptoms alone may come to be dominated by placebo reactions. That the field of clinical ecology may have developed disease and treatment concepts based on placebo responses is suggested by the increase in the number of placebo responses that are considered to be symptoms of disease. In 1976 Toogood, quoting Pogge, listed 22 nonspecific symptoms reported in response to the administration of a placebo in 67 clinical studies.[22] Of these 22 symptoms, only 5 were listed as symptoms of food allergy in 1951 by Rinkel and colleagues.[2] Today, 21 of the 22 symptoms commonly seen in response to placebo administration are considered to be indicators of "environmental hypersensitivity," including food sensitivity.

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