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Daniel C. Kline

YALE UNIVERSITY

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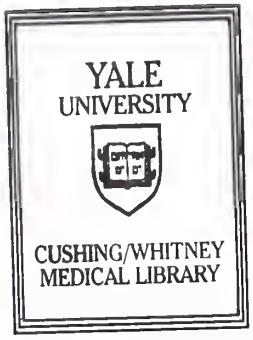
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Placebos and the Role of Expectancy in Nickel Patch Tests

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

Daniel C. Kline

2003

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ABSTRACT

Background: Allergens used for patch testing have shown variable reproducibility; data for nickel sulfate ($NiSO_4$) used in patch testing suggest a reproducibility rate of 80-95%. The reasons for variable patch test results are only partly understood. The placebo effect, a measurable physiologic response caused by the subject's expectation of a change in symptoms following treatment, may play a role in patch testing.

Objective: To further evaluate the reproducibility of $NiSO_4$ in patch testing and to assess the role of expectancy in patch testing and in allergic contact dermatitis.

Methods: Patch testing was performed on nine patients with a documented history of nickel allergy. Patches were applied to the lateral aspect of both upper arms; one arm received placebo (yellow petrolatum plus food coloring to match $NiSO_4$ color) while the other arm received $NiSO_4$. In the first test, patients were told the true identity of each patch. In the second test, performed six weeks later, patients were blinded to the true identity of each patch but were given expectancy on one arm.

Results: A positive reaction to the $NiSO_4$ was seen in both tests for eight of the nine patients with history of nickel sensitivity, confirming the reported rate of reproducibility. In the blinded test, five patients exhibited slight to moderate reactions to the placebo patch versus zero in the unblinded test.

Conclusion: While patch testing with $NiSO_4$ shows good reproducibility, expectancy may play some role in the manifestation of cell-mediated (delayed type) hypersensitivity. Further study with a larger population is warranted to confirm this finding.

ACKNOWLEDGEMENTS

This project has been a tremendously valuable experience for me. Thanks to the support of many in the Yale Medical School faculty, I was able to take my interest in the placebo effect and make a thesis out of it. The project started as a series of philosophical discussions with Dr. Howard Spiro in the department of medicine and led to a deep search of the literature on the placebo effect. I found an old, forgotten paper from Japan that pushed the limits of what even I thought would be possible. I didn't see that anyone had paid any attention to it or its incredible findings, and so I decided to challenge it with my own study. I carefully constructed a study design to get at the problem and received the approval of the Yale HIC to conduct what was a very ambitious and ethically complex clinical trial using human subjects. Thanks to the generous support of Dr. Kalman Watsky in the department of dermatology, I was able to pull potential subjects out of a logbook of clinic visits for contact dermatitis. I recruited eligible subjects and implemented the study protocol. With the surprising results that the study generated, I was able to publish an abstract and present the paper at a national meeting. The completion of this thesis marks the end of the project, but the experience is something that will continue to serve me throughout my career.

I thank Kalman Watsky, M.D. for his invaluable help in the clinical execution of this trial. I also thank Yale University and Howard Spiro, M.D. for their generous support in this study, and in particular Dr. Spiro for his guidance and academic support. I owe a debt of gratitude to Fran Mantiglia, R.N. for valuable assistance with the clinical aspects of the study and chart review. Finally, I thank Lisa Gibertoni, B.A. for her important contributions to placebo engineering and support with the blinding protocol.

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INTRODUCTION

The placebo effect is a puzzling phenomenon. Its legacy stretches back to the earliest records of healing practices. And it remains alive today both in medical research and practice, alongside hundreds of scientifically proven drugs and procedures. Yet, for its long tenure in the field of medicine, surprisingly little is known regarding its biological mechanisms, functions, and limits.

Even defining placebo proves to be an elusive goal, judging by the lack of consensus in the literature. A placebo at the most fundamental level is any type of treatment (e.g. a pill, an injection, connection to a medical device, a surgical procedure) that is administered to a patient that does not have a specific biochemical or anatomic target. Examples include sugar pills and injections of sterile water or saline. For the purposes of this study, the placebo response is defined as a measurable change in the body that occurs in response to the administration of an inert substance or procedure in the context of a medical intervention. Because by definition the drug or treatment is targetless and inactive in any direct way, the main determinant of the placebo response is the meaning that a patient takes from its administration. In other words, what gives the placebo any power that it has is the patient's expectation that his condition will improve from the treatment. Expectancy can be established by a nearly limitless number of psychological cues, including but not limited to the patient's experiences and convictions,

the doctor's office, the swallowing of a pill, the feel of an injection, attachment to a medical device or the dynamics of the doctor-patient encounter.

Closely related to the placebo responses is the concept of the nocebo. The familiar concept of the placebo effect may be described as a circumstance in which the patient expects an improvement in symptoms to be brought about by some form of treatment, and then that improvement is realized in the absence of any *real* treatment. The term nocebo refers to the converse scenario, where a healthy patient expects his condition to deteriorate, and then that deterioration is realized in the absence of any *real* insult.

The biological mechanisms for both placebo and nocebo effect are poorly understood, but it seems likely that illumination of one phenomenon could help elucidate the mechanisms of the other. Because of ethical considerations surrounding the administration of placebos to ill patients in the place of medications with proven efficacy, the nocebo represents an attractive proxy through which to test the role of expectancy in disease. The intensity of the insult conferred by the nocebo can be carefully controlled so that its effect is safe but still enough to generate a quantifiable physiologic response for analysis. When the study is completed, the nocebo is removed and the subject returns to his or her prior state of health.

Considering how little is known regarding the molecular pathways for placebo response, it is remarkable that the clinical findings are so robust. The most compelling evidence thus far has been in the areas of reactive airway disease, pain management, and allergy. In one oft cited study conducted by Luparello et al.[1], a normally innocuous bolus of nebulized saline was presented to asthmatic patients as an irritant or allergen and

triggered a significant increase in airway resistance in 47.5% of patients. For the 12 patients who reacted with a full-blown asthma attack, the same saline solution effectively resolved the crisis when presented subsequently as a bronchodilator. A control group of nonasthmatics were unaffected when exposed to the same treatment. The challenges raised by Lewis et al.[2] that the effects seen were due to airway cooling were refuted by a subsequent study by Neild and Cameron[3] who repeated the study using warmed saline and obtained similar results. Neild and Cameron additionally demonstrated, as others have[4], that the effects on forced expiratory volume in one second (FEV_1) of nebulized saline administered with suggestion of tightness or relief can be blocked by prior administration of an anticholinergic agent. Several other studies have similarly confirmed a psychogenic component of asthma[5], including a case report of one rose-sensitive patient who developed an asthma exacerbation when presented with a plastic rose[6].

Similarly striking results have been found regarding the impact of placebo effect on pain[7,8,9]. Administration of a placebo has been reported to result in a reduction in the reported intensity of pain compared to an untreated control group using both the category intensity scale[10] (a change from severe to moderate or from moderate to mild) and the visual analog intensity scale[11] (change by an average of 1 cm on a 10 cm scale). In a study of postoperative pain following extraction of the third molar, a hidden injection of 6-8 mg of morphine corresponded to an open injection of saline. The hidden injection did not exceed the analgesia brought about by the open injection of saline until the morphine dose was increased to 12 mg. The authors concluded that the analgesic effect of an open injection of saline, when offered for pain relief, is equivalent to 6-8 mg of

parenteral morphine[9,12]. Consequently, it is not surprising that the amount of analgesic required to relieve pain has been well documented to be considerably less when the analgesic is administered openly compared to when its administration is hidden from the patient[13,14]. In another study, patients who received a placebo booster believing it to contain analgesic require less pain medication to attain the same level of analgesia than patients who did not receive the placebo booster[15]. Several studies have implicated endogenous opioid release as a mechanism for the phenomenon of placebo analgesia by showing that naloxone either completely or partially blocks the effect of placebo analgesia, depending on the context of administration[9,11,16,17]. Recently, Petrovic et al.[18] used positron emission tomography (PET) to demonstrate that placebo analgesia causes the same changes to cerebral blood flow as those caused by the administration of remifentanil, a rapidly acting opioid agonist. The region affected, the rostral anterior cingulate cortex, has been implicated in opioid analgesia, throwing support behind the theory that placebo analgesia works by stimulating the body's endogenous opiate axis. Although the exact mechanisms though which placebos modulate pain are still not completely understood, the evidence for a psychogenic component to pain and analgesia is accumulating and the relationship is becoming more clearly established. This recent work demonstrates a connection between the cerebral cortex and deeper areas of the pain, such as those involved in pain.

So, too, are there connections between the brain, the immune system and the skin. Many dermatologic disorders, including warts and atopic dermatitis, have an immunologic component[19] and this interplay is probably related to the common ectodermal origin of neuro-immuno-cutaneo-endocrine structures. Specific

neuropeptides such as substance P and vasoactive intestinal peptide play a role in the pathophysiology of conditions like psoriasis and atopic dermatitis[20,21,22]. The involvement of these and other neuropeptides in skin pathology suggests a direct mechanism through which psychological stress may modulate skin disease, via the so-called psychoneuroimmunological pathway[23]. Psychological factors have been shown to influence or at least predict outcomes of wart treatment[24]. One study reported improved treatment outcomes for patients with warts who underwent hypnotic suggestion as compared to patients who received topical salicylic acid, placebo or no treatment[25].

One of the most startling examples of placebo effect or in this case, nocebo effect, lies in the study of allergy. One particular study, performed by Y. Ikemi and S. Nakagawa in 1962 at Kyushu University in Fukuoka, Japan, examined the possibility of eliciting allergic contact dermatitis using only the suggestion of an exposure to allergen[26]. The subjects were chosen from a population of 15-18 yr. old boys reporting a history of high sensitivity to *Rhus venicifera*, the urshiol-containing Japanese lacquer or wax tree; the reaction typically seen to *R. venicifera* is similar to that caused by the North American urshiol-containing variants including poison ivy (*Rhus radicans),* oak (*R. toxicodendron* and *R. diversiloba)* and sumac (*R. vernix).* In one phase of the study, 13 subjects were told to expect the leaves of a chestnut tree, the inert placebo or sham allergen, to be rubbed on one arm and the leaves of the lacquer or wax tree to be rubbed on the other. The subjects were then either blindfolded or hypnotized, at which time the patients' arms were treated with the leaves. The actual exposure to the urshiol-containing leaves was given on the arm where the patient expected to receive the harmless leaves, while the harmless leaves were rubbed on the arm the patient expected to be treated with

allergen. In all 13 cases, patients developed allergic contact dermatitis on the control-treated arm where the patient expected the allergen, while only two subjects also developed a reaction on the urshiol-treated arm. The study design could have been improved by the inclusion of a crossover trial, but its results are compelling even without this additional test. The remarkable work of Ikemi and Nakagawa suggests that the placebo effect may play an important role in the evolution of allergic skin reactions. To date, the Kyushu paper has not been challenged or replicated. If it can be shown that the phenomenon reported by Ikemi and Nakagawa can be reliably replicated, there would be striking implications in the field of allergy treatment, as well as new added support for the importance of reliable double-blinding for placebo-treated control groups in randomized drug trials.

In this study, I attempt to test the findings reported in the Ikemi and Nakagawa study. For ethical and safety reasons, I made some modifications to the experimental design used in the 1962 Japanese study. The work by Ikemi and Nakagawa used deception of minors (aged 15-18) in a temporal and cultural context much different from that which exists at Yale today. Current regulations, ethical guidelines, and university policies prohibit the use of explicit deception even on adults. This study uses adult volunteer subjects who agree to engage in a period of not knowing with respect to the actual identity of the test materials, answered with a complete disclosure of treatment identities at the conclusion of the study.

The allergen must be modified from the 1962 design, as well, as urshiol is not approved for clinical use or investigation on human subjects in the United States. Instead, my design uses nickel patch testing on subjects with a documented history of

nickel sensitivity to measure the role of expectancy in allergic contact dermatitis. Nickel allergy is quite common, with a prevalence in the United States population of 10%-15%, with a considerable female predominance[27]. Ear piercing with nickel-containing earrings is thought to be the sensitizing event and may explain the female predominance of the allergy. Typical exposure can often be traced to nickel-containing jewelry, buttons, zippers, and dental appliances. The occupational exposures most commonly seen in clinical practice are among patients employed as cashiers and retail clerks, hairdressers, painters, metalworkers, domestic cleaners, and caterers[28]. When nickel-sensitive individuals are exposed to nickel-containing alloys, the typical response is allergic contact dermatitis at the site of topical exposure. A Type-IV hypersensitivity delayed-type reaction, this allergic response carries no risk of serious systemic sequelae such as anaphylaxis. Because of the excellent safety profile of patch testing and because a reaction is readily visible, measurable and local, patch testing is a useful model through which to study the nocebo effect.

Patch testing is an important clinical tool that allows investigators to test for allergic sensitivity to a variety of allergens in a carefully controlled manner. Often in clinical practice, patients will present with a history and physical exam that suggests a diagnosis of allergic contact dermatitis. However, in many cases the offending agent cannot be definitively identified by history alone. Patch testing, a procedure that tests for sensitivity to specific allergens, presents a battery of common allergens as topical challenges over many small sites on the body. Sensitivity to a particular agent is suggested by the presence of a local dermatitic response in the distribution of the corresponding challenge patch.

For its theoretical utility, patch testing has assumed a central role in the diagnostic evaluation of dermatitis. Yet, despite its widespread use, patch testing remains an imperfect tool. Reliability problems include frustratingly high rates of false-positives and false-negatives and poor reproducibility of patch test results. Many aspects of patch testing have been examined as potential sources of error with the goal of improving test performance. These variables include uniformity of the test substance, amount of the test substance applied, number of tests applied, anatomic location of patch placement, duration of allergen exposure, and multiple patient parameters including sex, age, and atopy[29,30,31,32,33,34,35]. Unfortunately, even under close controls, reproducibility rates fall far short of 100%. Reproducibility in patch testing means that a patient demonstrates the same reaction to an allergic stimulus of a given strength and exposure duration each and every time it is presented. Different studies define the criteria of reproducibility differently; while some require reactions to be of same intensity score, others require only that a positive response is observed and allow for some variation in response intensity. By any criteria, there is a range of reproducibility among test substances, but even for nickel sulfate, one of the most reliable allergens, rates rarely exceed 80%[29,30,31,32]. This finding suggests that there remain undiscovered variables that significantly affect the results of patch testing.

One such factor could be expectancy. Compelling evidence of a psychogenic component to disease is in the literature of irritable bowel syndrome[36,37,38,39,40,41,42,43,44], pain management[7,8,10,11,12,16] and reactive airway disease[1,5,6]. Ikemi and Nakagawa first proposed the possibility of a psychogenic component in contact dermatitis in 1962 in which Urshiol-sensitive subjects developed allergic contact dermatitis by only the

suggestion of exposure to that allergen[26]. However, a Medline search revealed no recent work examining the relationship between expectancy and contact dermatitis or between expectancy and patch test outcome.

In this study, I attempt to determine the role of expectancy in allergic contact dermatitis by administering patch tests with nickel sulfate or placebo to subjects with known nickel sensitivity.

MATERIALS AND METHODS

Subjects

Yale Dermatology Clinic patients over 18 years of age with a history of nickel sensitivity were eligible for the study. History of nickel sensitivity was defined as a documented positive nickel patch test accompanied by a record of a high clinical suspicion for nickel allergy. Exclusion criteria included history of immune disorders other than allergy, history of psychiatric disorders, and current treatment with topical or systemic corticosteroids or other immunosuppressive agents.

A chart review was conducted of patients receiving patch tests at the Yale Dermatology Clinic from 1991-2000, and those meeting the selection criteria were culled. Invitations to participate in the study were offered by mail to forty-six patients. Fifteen subjects gave informed consent and were enrolled in the study. Remuneration was offered in the amount of $20/visit to cover travel costs. The Yale Human Investigation Committee approved the subject recruitment process and experimental procedure (appendix 1). All subjects were told of the possibility of deception during the course of the study in the process of obtaining informed consent for participation (appendix 2)

Methods

Each subject underwent two trials of patch testing separated by a washout period of at least six weeks. In both trials, Finn chambers on scanpor tape were used for patch testing and were applied to the lateral aspect of the upper arm. The allergen was 2.5% nickel sulfate ($NiSO_4$) in white petrolatum; the placebo was yellow petrolatum mixed with food coloring (FD & C Blue 1 with 0.1% propylparaben) to match the color of the $NiSO_4$. A standard 5 mm strip of ointment was applied to the Finn chamber discs.

The first trial was administered to confirm the nickel allergy. Each subject received a patch with two chambers on each arm. One of these chambers contained ointment and the other was empty. On one arm, the ointment loaded on the disc was $NiSO_4$ and on the other arm the ointment used was the placebo. Left and right were determined randomly for each subject using the coin flip method. In this test, the subjects were told truthfully which substance was which. They then watched as the syringes containing the ointments were presented, the patches were prepared, and then the patches were applied. They were told very precisely, "This is the placebo patch, it is only Vaseline and blue food coloring. It has no effect. I'm putting it on your RIGHT (or LEFT) arm." They were then told, "This is the patch with nickel on it. I'm putting it on your LEFT (or RIGHT) arm. You'll probably have a reaction to this patch that is similar to the reactions you've had in the past to nickel." Subjects were instructed to keep the patches on and dry for 48 hours and to return to the office at 72 hours for scoring. They

were permitted to wash the site after 48 hours had expired, but were asked not to apply any topical treatment until after the follow-up appointment, at which point they were provided with low potency steroid cream for symptomatic relief.

Subjects who demonstrated continued nickel sensitivity with a positive nickel patch test in trial one were included in trial two. In the second trial, the patients were again given the $NiSO_4$ patch on one arm and the color-matched placebo patch on the other. Left and right were determined randomly by the coin flip method. In this trial, however, the labels attached to the syringes identifying one as $NiSO_4$ and the other as placebo were assigned randomly for each subject. The technician preparing and applying the patches did not know whether the labels were correct or reversed. Expectancy was established by using the same procedure and language in the second trial as had been used in the first, with the addition of the phrase "I am told" before giving the identity of each ointment. They were told very precisely, "I am told that this is the placebo patch, it is only Vaseline and blue food coloring. It has no effect. I'm putting it on your RIGHT (or LEFT) arm." They were then told, "I am told that this is the patch with nickel on it. I'm putting it on your LEFT (or RIGHT) arm. You'll probably have a reaction to this patch that is similar to the reactions you've had in the past to nickel." Subjects were given the same instructions for patch care and returned at 72 hours for scoring, at which time they received topical treatment as needed.

Upon completion of the study, all subjects were debriefed thoroughly and the true identity of each test substance was revealed.

RESULTS

Fifteen subjects were enrolled in the study. All were female with a median age of 53 with a range of 28-83 (table i). The disproportionate participation by women was unintentional, as men were also eligible. However, the higher prevalence of nickel-related contact dermatitis among women was reflected in the selection pool: of 46 initial candidates, 38 were female versus 8 male. Those enrolled had a confirmed record of a positive nickel patch test scored as 1+ or greater between 1993 and 2000.

The purpose of the first trial was to confirm the persistence of nickel sensitivity in the subjects. Each subject also received a placebo patch on the arm opposite the $NiSO_4$ patch. A positive reaction to the $NiSO_4$ patch was seen in 12 of 15, or 80%, of the subjects tested (table ii). Reactions were scored in accordance with the International Contact Dermatitis Research Group classification[45,46]. There were two trace reactions, five 1+, three 2+ and two 3+ reactions. None of the subjects developed a response to the empty chambers or to the chamber loaded with blue petrolatum. The three subjects with no reaction to the $NiSO_4$ were eliminated from the study and three more were lost to follow-up.

Six weeks later, nine subjects completed the second trial. Through randomization, six received the $NiSO_4$ patch on the same arm as in the first trial and three subjects received it on the opposite arm (table ii). The $NiSO_4$ was given with true expectancy (the ointment presented as $NiSO_4$ actually was $NiSO_4$) for five subjects and with false expectancy (the ointment presented as placebo actually was $NiSO_4$) for four

subjects. In this trial, eight of nine or 88% of subjects reacted to the $NiSO_4$ patch (figure i). In addition, five of nine or 55% of subjects reacted to the placebo patch with either a trace or 1+ reaction (fig. i). Among these five subjects was the subject ("H") who did not react to the $NiSO_4$ patch in this trial; the other four had a concurrent reaction on the other arm to the $NiSO_4$ that was the similar to their reaction to the placebo. Of note, the blue dye in the placebo mixture left a bluish tinge to the skin at the site where it had been applied and this was not counted as a reaction, but it did serve to confirm the location of the placebo patch. There was no uniform relationship among this group with respect to site of $NiSO_4$ (same arm as in trial one or opposite) or site of expectancy (same arm as $NiSO_4$ or opposite); no statistical analysis was performed because of the small sample size.

DISCUSSION

To assess the effect of expectancy on allergic contact dermatitis and patch test outcomes I administered serial patch tests of $NiSO_4$ versus placebo. Multiple reports have shown $NiSO_4$ to be among the most reliable of allergens, with a reproducibility rate near 80%. I chose $NiSO_4$ as the test stimulus because its reliability suggests that there are relatively few factors that can affect the allergic response to $NiSO_4$ when administered to a nickel-sensitive subject. Therefore, I suspected that $NiSO_4$ patch testing would be quite resistant to the effects of psychogenic forces. It follows, however, that if expectancy could be shown to play a role in even $NiSO_4$ patch testing, then the psychogenic pathway for dermatitis may be quite robust.

The first result was a confirmation of the reliability of $NiSO_4$ patch testing. In trial one, 80% of subjects with a prior positive $NiSO_4$ patch test responded again to the $NiSO_4$ patch. This finding is consistent with previous reports[29,30,31,32]. Trial two challenged the responders with another $NiSO_4$ patch, this time with either true or false expectancy. Again, the $NiSO_4$ patch showed good reliability with a response rate of 88%. Reproducibility in this analysis was judged as simply positive/negative and not based on the relative strength of reaction. This analysis was chosen because the I read and scored the reactions myself and, without residency training in dermatology, felt confident in judging whether a reaction was present of absent but not always in deciding whether a reaction was a 1+ or a 2+, for example.

The incidence of reactions to the placebo-loaded patch test in trial two are noteworthy. Eight of nine subjects responded to the $NiSO_4$–loaded patch and five of nine responded to the placebo-loaded patch. There are several possible explanations for this response. First, the reactions could represent an ectopic flare of nickel-related contact dermatitis. The likelihood of this etiology is remote, given that three of the five subjects reacting to the placebo reacted on an arm that had never been exposed to a $NiSO_4$ patch. An ectopic flare at a nickel-naïve site is unlikely[47]. A second possibility is that the $NiSO_4$ and placebo patches were inadvertently reversed during trial two, when their true identities were masked. This, too, is unlikely considering that the blue dye was partially absorbed into the skin beneath the placebo patch, leaving a faint blue mark even after the patch was removed. This mark was noted for each patient and corresponded correctly to the designated placebo arm in all cases. Finally, there is the possibility that the dye itself had allergenic properties. A Medline search on FD&C Blue 1 was conducted and returned no reports of hypersensitivity reactions. The preservative mixed with the dye, propylparaben, has been implicated in a number of cases of contact dermatitis, however[48].

Propylparaben sensitivity was probably not the cause for the reactions to the placebo ointment. All of the subjects tested in trial two had a prior negative patch test to 15% paraben mix, a much greater concentration than that used in this study (table i). In addition, none of those subjects developed an allergic or irritant response to the placebo ointment in trial one. Without prior signs of paraben allergy, the only way that the five placebo responders in trial two could have been reacting to the propylparaben would be if they had been sensitized by trial one. It is unlikely, however, that they were sensitized by

a patch containing at most 0.1% propylparaben and applied to healthy, intact skin. In reports, a concentration 12 times that was required to sensitize 1/98 subjects and a concentration 100 times more potent failed to sensitize any of 96 more recipients[49,50,51].

The appearance of placebo reactions in the second trial can be attributed to the major difference between the first and the second trial: expectancy. Contact dermatitis was caused by an inert stimulus that was presented as a potent allergen. The phenomenon of contact dermatitis to a sham allergen was first reported 40 years ago in a study in which subjects reacted to inert Chestnut tree leaves when they expected exposure to urshiol-containing leaves of the Japanese Lacquer Tree (*Rhus venicifera)*[26]. Surprisingly, not all of the subjects who reacted to placebo ointment were given false expectancy. It is possible that some of the subjects believed they were being told the truth about the test substances while others believed the opposite. I cannot know what each subject believed at the time that she received the second patch test. I did not think to ask them at the time of the follow-up visit which site they believed had received placebo and which site the nickel-containing patch. In addition, it is possible that some of the subjects had noticed the blue stain on the skin under one of the patches (the placebo) and had drawn conclusions from that additional piece of information. The stain could only have been noticed 24 hours before the follow-up visit if the instructions regarding patch-care were observed, which would have minimized the influence of this "clue". In keeping with Yale HIC policies, all subjects were told of the possibility of deception in the second trial in the process of obtaining informed consent for participation (unlike in the 1962 study). Which subjects attempted to guess the labeling in the second trial is unknowable, but the imperfect correlation between placebo reaction

and expectancy can be explained by the possibility that some believed the information they were given while others did not.

Obviously, my study is underpowered and I am reluctant to offer conclusions based on statistical analysis of the results. However, I believe that my findings are nonetheless relevant and important, for they reveal the very high likelihood that expectancy exerts real influence on allergic contact dermatitis and, consequently, the results of patch testing. More significant than the number of subjects who reacted to placebo when expecting to receive allergen is the observation that *any* subject could manifest such a response to expectancy alone.

This study has shown that patients with a history of nickel sensitivity and positive $NiSO_4$ patch tests can develop contact dermatitis to an inert stimulus when they expect to receive $NiSO_4$. This finding suggests that expectancy can affect the outcome of patch testing, possibly contributing to the incidence of false-positives. The cellular mechanism for placebo-induced contact dermatitis may be related to connections within the neuro-immuno-cutaneous-endocrine network,[52] which may spring from the common ectodermal origin of these structures. Further study using novel allergens on a larger patient population is warranted to confirm these findings. Biopsy of local reactive tissue may also be helpful in clarifying the cellular mechanisms behind placebo-induced contact dermatitis.

The results of this study represent a meaningful contribution to the ongoing debate surrounding the placebo effect. Despite the studies reviewed earlier that present compelling evidence behind a robust placebo effect in the fields of asthma, pain

management and allergy, there remains a steady resistance to the proposition that the placebo effect accounts for anything at all. Recent arguments against the existence of a truly measurable placebo effect, such as those voiced by Hróbjartsson and Gøtzsche[53] center on the question of confounders. They assert that the placebo effect is a poorly defined term, which many take to mean the "difference from baseline in the condition of patients in the placebo group of a randomized trial after treatment" (p. 1594). They object to this application of the term on the grounds that, in this case, the natural course of the disease is more likely to explain the difference from baseline for this population.

They are correct in their assertion. In studies of diseases that have a natural course of exacerbation and recovery or of those that have an unknown natural course, there is no way to distinguish the placebo effect from the natural progression of the untreated disease. Because few studies use a no-treatment group, there is often no group of patients with whom to compare the outcomes in the placebo group to detect any differences from natural progression. Care must be taken not to misattribute outcomes in the placebo group of a disease that follows an uncertain or fluctuating natural course to the placebo effect. Any important study that offers conclusions in support of the placebo phenomenon will have accounted for this variable by using novel approaches to measure the difference between the placebo group and a no-treatment group.

A second objection raised to the implication of the placebo effect in health outcomes across disciplines is reporting bias. The argument is that subjects in studies are likely to report improvement because of a tendency to try to please the investigator even when no true improvement has occurred[53,54]. Subjective outcomes (e.g. improvement of

pain) are particularly susceptible to this kind of bias, while objective ones (e.g. changes in bloodflow) are more resistant.

These objections suggest that the placebo effect may be entirely artifact, its "effects" accounted for entirely by a combination of the natural course of disease and reporter bias. Could the placebo effect simply be a manifestation of the Hawthorne effect, a clinical phenomenon akin to the Heisenberg Uncertainty Principle in physics, whereby the very act of studying something causes it to change? Perhaps patients who participate in studies do better than patients who do not participate in studies, no matter what the intervention. In order for the placebo effect to be studied in a rigorous way, a good study design is essential to minimizing bias and to differentiate between placebo-related outcomes and any number of confounders.

The study I conducted here provides an example of how studies can be designed to minimize the risk of bias and confounding. I used a blinded protocol where each patient served as her own control. The outcome was an objective one that could be scored by a blinded investigator. And by using a nocebo on otherwise healthy but sensitive subjects, there was no way for the natural course of the disease to account for the outcome I measured. Through careful design, I feel confident that the results obtained in this study represent a true response to a nocebo insult, though the mechanism for this response is not yet clear.

So what of randomized controlled trials (RCTs) with high numbers of placebo responders? With few no-treatment groups, it is difficult to interpret the results in a generalized way. Rather, studies should be interpreted on a case-by-case basis. Moyad

2002 in table iii[55] reviews the literature of 11 oft-studied ailments and reports the mean percent of placebo responders by ailment. Placebo response approaching 50% is seen in ailments as diverse as alopecia, benign prostatic hypertrophy, depression, erective dysfunction, gastroesophageal reflux disorder and hot flashes associated with menopause. Many of these ailments have natural histories with waxing and waning intensities, and the distinction between true placebo response and simple episodic fluctuations in disease course will require considerable and rigorous study. However, the report raises important questions about the standards and interpretation of clinical trials.

Studies of diseases that are known to have a high rate of placebo response face a difficult statistical challenge. The current gold standard in trial design is the randomized double-blind placebo-controlled trial, where the mark of effectiveness is in the difference between the outcomes in the experimental group and the control (placebo) group. Diseases in which the placebo group often shows response rates approaching 50% require much higher rates of drug response and much larger sample sizes to achieve satisfactory power and statistical significance compared to diseases with lower rates of placebo response. The addition of a true no-treatment group to these studies would be helpful in assessing the true magnitude of both the response truly due to placebo and that due to the experimental drug under investigation. Clearly the use of no-treatment groups is a design that would require ethical review on a case-by-case basis. For all its utility in the study of disease, placebo and treatment, the withholding of effective medical treatment required in the study of the natural course of disease represents a complicated conflict between the interests of the patient and the advancement of medical knowledge.

In fact, the use of placebo control groups has come under similar fire from ethics committees in recent years, many of them arguing that a more appropriate baseline for comparison of an experimental drug is the current best traditional therapy. While at first approximation this idea seems reasonable for its preservation of the subjects' interests, it adds a layer of dangerous complexity to the interpretation of study data. Consider the outcome of the Hypericum Depression Trial Study Group[56], a multi-center prospective double blind placebo-controlled randomized trial published in JAMA in 2002. The study compared St. John's wort with sertraline and placebo for the treatment of major depressive disorder. There were two main findings. First, all three groups of patients demonstrated improvement over the eight-week study, measured by the Hamilton Depression Scale. Second, in one measure of full response, the Global Clinical Improvement score, the patients in the placebo group did considerably better than those in both the sertraline and St. John's wort groups. Their conclusion was that St. John's wort is not effective since it did not demonstrate statistically significant improvement over placebo. However more interestingly, if the study had not included a placebo group and, instead, had compared St. John's wort to only sertraline, a "proven effective therapy," then the conclusion of the study would have been that St. John's wort is as effective as sertraline! In fact, the study was underpowered and was of too short duration, in addition to other methodological shortcomings, but it nicely reminds us of the risks of excluding a placebo control group from the design. Others have noted these implications of the Hypericum study as well[57,58].

The Hypericum study brings to light several other issues in the consideration of the placebo effect. Were the results seen in the placebo group simply a reflection of

Hróbjartsson and Gøtzsche's triad of the natural history of the disease (major depression), regression to the mean, and reporter bias? Or is there a measurable improvement in patients who receive placebo treatment with the medical context that it implies? The Hypericum study cannot answer the question, as it neglected to include a no-treatment group for comparison. However, a good deal of circumstantial evidence suggests that a veritable placebo effect may have been at work in their study. Over the past 20 years, the effectiveness of pharmacologic treatment of depression has improved dramatically. In a meta-analysis of 75 controlled trials for depression, Walsh et al.[59] found that the proportion of patients responding to tricyclic antidepressants and to selective serotonin reuptake inhibitors has increased from approximately 40% to 55%. In a parallel fashion, the proportion of patients responding to placebo for depression has increased over the same period from 20% to 35%[59]. Furthermore, the year of study publication is strongly correlated with the proportion responding to both drug and placebo. These data suggest that the increase in apparent effectiveness of antidepressants over this period can be attributed to the growing placebo effect that is superimposed on the drug's targeted pharmacologic activity. Moerman[58] suggests that the increasing consciousness of doctors, patients and their friends via newspapers, journals and television that depression can be treated with drugs accounts for some of this change. This awareness was not present 20 or 25 years ago. If this is, indeed the case, then the increases in response of depression to placebo (and to antidepressant) over this period is not a statistical artifact as Hróbjartsson and Gøtzsche might suggest[53], but instead, a real improvement in outcome arising from a treatment potentiated by positive expectations.

The possibility that this is, in fact, the explanation for the improvements in outcome seen over the past 20 years will require rigorous study with at least 3 treatment arms: drug, placebo and no-treatment. Though improvements in the treatment of depression seem likely to be related to increasingly positive expectations of patients receiving treatment, it is possible that the type of depression seen over the same 20-year period has changed, instead. The diagnostic criteria have changed over that period such that a diagnosis of depression means something different today than it did 20 years ago. The natural course of a depressive episode as it is defined today could be shorter than it was 20 years ago, with measurable improvement occurring naturally within the period of time that a subject is under study. Particularly in the case of antidepressant medications, where efficacy over placebo has been so difficult to establish, the comparison with a no-treatment group is important to provide a meaningful baseline against which the effect of treatment can be compared. Placebo groups by definition receive an inert substance; it is the meaning of the pill or injection in the context of medical treatment that creates the state of expectancy that brings about a physiologic response. A no-treatment group, to be an accurate baseline completely protected from even the Hawthorne effect, should be selected prospectively at the start of the study and consented in a general way to determine if the patient would be willing to participate in a study of observation only. So long as subjects in all three arms are followed closely and data analyzed as they return such that the study could be terminated at the earliest sign of benefit, the ethical ramifications of such a design do not deviate from those of a traditional two arm (placebo and experiment group) study.

Another methodologic difficulty with the convention of testing a new treatment against the prevailing traditional therapy without inclusion of placebo and/or no-treatment groups relates to the placebo factor present in active therapy. Because the response to a placebo is based on the medical context surrounding treatment, subjects in the active therapy arm of a blinded study receive the same amount and type of expectancy as those in the placebo group. Whatever placebo response results from this interaction is superimposed on the targeted pharmacologic and/or physiologic effects of the active agent. Some agents provide such a narrow advantage over placebo that enormous sample sizes are required to generate a study with enough power to detect statistically significant differences between the experimental drug and placebo. Antidepressants provide one example of this phenomenon, another is H_2-blockers. Analyses of RCTs demonstrating the effectiveness of H_2-blockers showed that only studies with low rates of placebo response were able to demonstrate the effectiveness of the drug[60,61]. The result these studies of H_2-blockers depended on the magnitude of the placebo response as well as the response to the active agent.

The magnitude of the placebo response depends on many variables, some known and many undescribed. As seen in the examples of antidepressants and H_2-blockers, the size of the placebo response can influence the results of clinical trials. One of the determinants of placebo response level is the type of sham treatment that is administered as the placebo. In a study of the acute treatment of migraine, subcutaneously injected placebo analgesia was found to be more effective than placebo pills taken by mouth[62]. Another study found a predictable relationship between the type of sham treatment and the scale of placebo response, revealing that sham surgical procedures have the highest

response rate, followed by connection to medical devices (turned off when connected), then placebo injections and finally pills[63]. This finding should be remembered when interpreting the results of trials that compare a surgical intervention to medical treatment. Such a study should probably include both sham surgery and medical placebo groups in addition to a no-treatment group if feasible, to control for a baseline that may act as a moving target depending on the placebo intervention used for comparison.

In the present study, I offer evidence that contact dermatitis should be included in the growing catalog of diseases in which expectancy plays an active role. Despite the continued accumulation of evidence in support of the phenomenon commonly known as the placebo effect, many in the medical and scientific community resist the notion of a connection between the mind and health. With continued study, I am hopeful that the mechanisms for these connections will be uncovered and that these connections can eventually serve as new targets in the treatment of illness and disease. Until that time, we must take the utmost care to control for the potentially far-reaching impact of the placebo effect when deciding the methodologic design of clinical trials. Only by so doing can we be confident that we are, in fact, testing what we claim to be.

TABLES AND FIGURES

Subject	Age	Sex	Date of nickel allergy diagnosis	Score of Diagnostic 5% $NiSO_4$ Patch Test	Score of 15% Paraben Mix Patch Test
A	46	F	5/6/1999	2+	N.R.
B	57	F	4/7/1994	2+	N.R.
C	68	F	2/11/1993	1+	N.R.
D	53	F	9/3/1998	1+	N.R.
E	67	F	5/2/1991	2+	N.R.
F	43	F	12/4/1997	1+	N.R.
G	52	F	10/24/1991	2+	1+
H	58	F	6/8/2000	1+	N.R.
I	46	F	7/23/1998	1+	N.R.
J	53	F	5/7/1998	3+	N.R.
K	65	F	2/3/1994	1+	N.R.
L	59	F	5/30/1991	3+	N.R.
M	28	F	9/11/1997	2+	N.R.
N	28	F	5/6/1999	1+	N.R.
O	83	F	5/6/1993	2+	N.R.

Table i - Subject characteristics

Subject		Trial 1				Trial 2		
	Reaction to $NiSO_4$	Reaction to placebo	Site of $NiSO_4$		Site of $NiSO_4$	Site of expectancy	Reaction to $NiSO_4$	Reaction to placebo
A	Tr	N.R.	Left arm		Left	Left	1+	Tr
B*	2+	N.R.	Left		-	-	-	-
C†	N.R.	N.R.	Left		-	-	-	-
D†	N.R.	N.R.	Right		-	-	-	-
E	2+	N.R.	Left		Right	Right	2+	Tr
F	1+	N.R.	Left		Left	Left	1+	N.R.
G*	3+	N.R.	Left		-	-	-	-
H	1+	N.R.	Right		Right	Left	N.R.	1+
I†	N.R.	N.R.	Left		-	-	-	-
J	3+	N.R.	Left		Left	Right	3+	N.R.
K	2+	N.R.	Right		Left	Left	1+	1+
L	1+	N.R.	Right		Right	Left	1+	Tr
M	1+/2+	N.R.	Left		Left	Right	1+	N.R.
N*	1+	N.R.	Left		-	-	-	-
O	Tr	N.R.	Left		Right	Right	Tr	N.R.

* Subjects B,G,N lost to follow-up.

† Subjects C,D,I disqualified for failure to confirm nickel allergy.

Table ii - Results trials 1 & 2

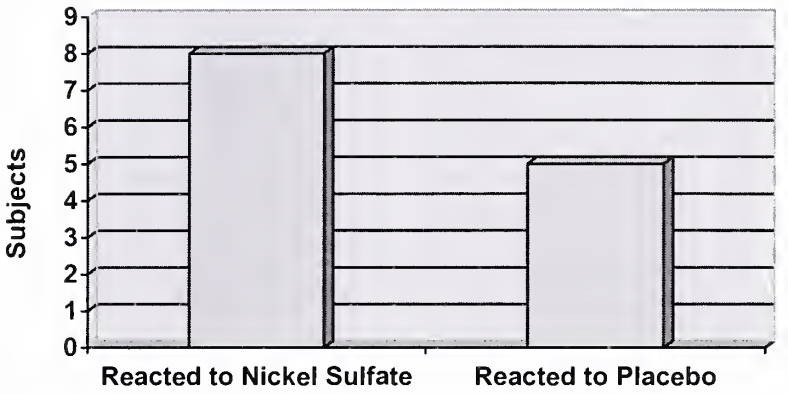

Figure i - Results of trial 2.

Various medical conditions successfully treated with conventional medical agents and the observed approximate placebo response from these randomized controlled trials

Condition	Placebo response
Allergies/Asthma	10–20%
Alopecia (hairloss/premature baldness)	7–45%
BPH	25–50%
Cholesterol lowering (statins)	~1–1%
Depression or social anxiety disorder	20–40%
ED	25–40%
GERD and related conditions	15–50%
Hot flashes	20–50%
Osteoporosis	~5–0%
Pain	20–35%
Weight loss	5–15 lbs
Overall range of placebo response	~5–50%

Numbers reported are mean reductions in the placebo group for allergies/asthma, cholesterol lowering, bone mineral density (osteoporosis), and weight loss. Other placebo responses reported above are approximately the percentage of patients in the placebo group that experienced a response that was equivalent to that observed with the conventional treatment. The only conditions above with truly objective measurement outcomes are cholesterol lowering, osteoporosis, and possibly weight loss in some trials.

Abbreviations: BPH, benign prostatic hyperplasia; ED, erectile dysfunction; GERD, gastroesophageal reflux disease.

Table iii – Rates of placebo response in literature by disease (borrowed from Moyad[55])

APPENDIX 1 – Yale Human Investigation Committee Protocol

II. DESCRIPTION OF STUDY

A. **Purpose:** Placebo treatment, characterized by the administration of an inert substance along with a positive suggestion of healing, has been the subject of intense debate over the last decade or longer. This study aims to focus the debate by use of a relatively harmless allergen, the metal nickel, which is often found in jewelry, buttons, zippers, and other clothing accessories. Adult, volunteer subjects with established nickel allergy will be exposed to varying combinations of suggestion, sham exposure to allergen, and real exposure to allergen in an effort to determine if suggestion can trigger an allergic contact dermatitis reaction to an inert substance (petrolatum).

B. **Background:** The placebo effect is a puzzling phenomenon. Its legacy stretches back to the earliest records of healing practices. And it remains alive today both in medical research and practice, alongside hundreds of scientifically proven drugs and procedures. Yet, for its long tenure in the field of medicine, surprisingly little is known regarding its biological mechanisms, functions, and limits.

Even defining "placebo" proves to be an elusive goal, judging by the lack of consensus in the literature. For the purposes of this study, the placebo response will be defined as an observable physiologic change in the body that can be elicited by a pharmacologically inert substance. Because by definition the drug or treatment administered is inactive, the main determinant of the placebo response is the patient's own expectancy. Expectancy is established by a nearly limitless number of psychological cues, including but not limited to the patient's history with medicine, the doctor's office, the size or shape or color of a pill, the feel of an injection, or the dynamics of the doctor-patient encounter.

One further issue that must be described with respect to placebo responses is the concept of the nocebo. The familiar concept of the placebo effect may be described as a circumstance where the patient expects a positive health outcome to be brought about by some form of treatment, and then that positive outcome is realized in the absence of any *real* treatment. The term nocebo refers to the converse scenario, where a healthy patient expects to receive some insult to health, and then that negative outcome is realized in the absence of any *real* insult.

The biological mechanisms for both placebo and nocebo effect are poorly understood, but it seems likely that illumination of one phenomenon could help elucidate the mechanisms of the other. Because of the ethical concerns regarding the administration of a placebo to a sick patient where proven pharmacologically active drugs already exist, this study will be strictly limited to examining a low-impact nocebo effect in otherwise healthy patients.

Considering how little is known regarding the molecular pathways for placebo response, it is encouraging that the clinical findings are so robust. The most compelling

evidence thus far has been in the areas of asthma, pain management, and allergy. In one oft cited study[i], a normally innocuous bolus of nebulized saline was presented to asthmatic patients as an irritant or allergen and triggered a significant increase in airway resistance in 47.5% of patients. For the twelve patients who reacted with a full-blown asthma attack, the same saline solution effectively resolved the crisis when presented subsequently as a bronchodilator. A control group of nonasthmatics were unaffected when exposed to the same treatment.

Similarly striking results have been found regarding the impact of placebo effect on pain management[ii]. Administration of a placebo has been reported by multiple sources to result in a reduction in pain reported (when compared to a untreated control group) using both the category intensity scale (e.g. severe to moderate or moderate to mild)[iii] the visual analog intensity scale (by an average of 1 cm on a 10 cm scale)[iv]. In one study, placebo analgesia was found to be equivalent to roughly 5 mg of morphine administered intravenously[v]. Again, though the effects of placebo dosing are robust, the specific mechanisms responsible for the phenomenon are not entirely known (although endogenous opioid release has been implicated in several studies[vi]).

The most startling examples of placebo (or in this case nocebo) effect lie in the study of allergy. One particular study, performed by Y. Ikemi and S. Nakagawa in 1962 at Kyushu University in Fukuoka, Japan, looked at the possibility of eliciting allergic contact dermatitis with only the suggestion of an exposure to allergen[vii]. The subjects were chosen from a population of 15-18 yr. old boys reporting a history of high sensitivity to the Japanese lacquer or wax tree, a plant causing a similar reaction to that caused by poison ivy. In one phase of the study, 13 subjects were told to expect the leaves of a chestnut tree (the inert control, or placebo) to be rubbed on one arm and the leaves of the lacquer or wax tree to be rubbed on the other. The subjects were then either blindfolded or hypnotized, at which time the patient's arms were treated with the leaves. The actual exposure to the irritant leaves was given on the arm the patient expected to receive the harmless leaves, while the harmless leaves were rubbed on the arm the patient expected to be treated with irritant. In all 13 cases, patients developed dermatitis (e.g. itching, erythema, papules, and vesicles) on the control-treated arm where the patient

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[i] Luparello, T. J., H. A. Lyons, E. R. Bleecker, and E. R. McFadden. 1968. "Influences of Suggestion on Airway Reactivity in Asthmatic Subjects." *Psychosomatic Medicine*, 30:819-825.

[ii] Gelfand, S., L. P. Ullmann, and L. I. Krasner. 1963. "The Placebo Response: An Experimental Approach." *J. Nerv. Mental Diseases*, 136:379-387.

Gracely, R. H., R. Dubner, P. J. Wolskee, and W. R. Deeter. 1983. "Placebo and Naloxone Can Alter Post-surgical Pain by Separate Mechanisms." *Nature*, 306(17):264-265.

Levine, J. D., and N. C. Gordon. 1984. "Influence of the Method of Drug Administration on Analgesic Response." *Nature*, 312(5996):755-756.

[iii] Liberman, R. 1964. "An Experimental Study of the Placebo Response Under Three Different Situations of Pain." *J. Psychiat. Res.*, 2:223-246.

[iv] Grevert, P., L. H. Albert, and A. Goldstein. 1983. "Partial Antagonism of Placebo Analgesia by Naloxone." *Pain*, 16:129-143.

[v] Levine, J. D., N. C. Gordon, R. Smith, and H. L. Fields. 1981. "Analgesic Responses to Morphine and Placebo in Individuals with Postoperative Pain." *Pain*, 10:379-389.

[vi] Fields, H. L. and D. D. Price. 1997. "Toward a Neurobiology of Placebo Analgesia." In: A. Harrington (ed.) "The Placebo Effect: An Interdisciplinary Exploration." Cambridge: Harvard University Press.

[vii] Ikemi, Y. and S. Nakagawa. 1962. "A Psychosomatic Study of Contagious Dermatitis." *Kyushu J. of Med. Sci.*, 13:335-350.

expected irritant, while only 2 subjects also developed a reaction on the irritant-treated arm.

Clearly, the work of Ikemi and Nakagawa widens the scope of what suggestion and placebo treatment can accomplish. To date, the Kyushu paper has not been challenged or replicated. There is an interest, both on the part of hopeful advocates for continuing placebo research[viii] as well as skeptical research dermatologists at Yale[ix] to see the work reproduced. If it can be shown that the phenomenon reported by Ikemi and Nakagawa can be reliably replicated, there would be striking implications in the field of allergy treatment, as well as new added support for the importance of reliable double-blinding for placebo-treated control groups in randomized drug trials.

This study will attempt to loosely replicate the Ikemi and Nakagawa study. For ethical and safety reasons, some modifications will be made to the experimental design used in the 1962 Japanese study. The work by Ikemi and Nakagawa used deception on minors (aged 15-18) in a temporal and cultural context much different from that which exists at Yale today. Current regulations, ethical guidelines, and university policies prohibit the use of deception even on adults, but that need not be the end of this inquiry.

The work at Yale will be conducted instead on adult, volunteer subjects with a documented, preexisting sensitivity to nickel. The subjects will be selectively exposed to a standardized nickel allergen used in routine dermatologic patch testing. They will also be exposed to a sham allergen, consisting of nothing more than the inert anhydrous vehicle petrolatum. With respect to information regarding the true identity of treatment received, subjects will be solicited for consent to engage in a period of not knowing, answered with a complete disclosure of treatment identities at the conclusion of the study.

Nickel allergy is quite common, with a prevalence rate estimated at 10%-15%[x]. Nickel is contained in a large variety of everyday items, including jewelry, buttons, zippers, and dental appliances. Nickel allergy is characterized by the development of an allergic contact dermatitis at the site of topical exposure and is most common in women, where sensitization is suspected to occur as a consequence of ear piercing.

C. **Specific Location of Study:** Yale Dermatology Clinic, 4th Floor, Yale Physicians Building, 800 Howard Avenue, New Haven, CT. Hope Building, Yale School of Medicine, 333 Cedar Street, New Haven, CT.

D. **Probable Duration of Study:** June, 2000 to October, 2000.

[viii] Kirsch, I. 1997. "Specifying Nonspecifics: Psychological Mechanisms of Placebo Effects." In: A. Harrington (ed.) "The Placebo Effect: An Interdisciplinary Exploration." Cambridge: Harvard University Press.

[ix] Watsky, K. Personal Communication. 2000.

[x] Rietschel, R.L. and J. F. Fowler, (eds). 1995. "Fisher's contact dermatitis," ed 4. Baltimore: Williams & Wilkins.

E. Research Plan: Only patients with a history of sensitivity to nickel and a confirmed record of a positive nickel allergen patch test will be eligible for this study.

After an eligible patient has been invited and has agreed to participate, a careful history of the patient's specific exposures to and attitudes towards nickel and the reaction it elicits in him or her will be taken. The patient will be asked to score his or her own sensitivity to nickel along a categorical scale ranging from minimal sensitivity to highest sensitivity.

1st Treatment: The purpose of the first treatment is to confirm allergy and to establish/strengthen the patient's belief in the potency of the test solutions. All subjects will be treated on one arm (upper arm and back are the customary sites for nickel allergen patch testing) with a standard concentration (2.5%, petrolatum-based) nickel-sulfate test solution and on the other arm with the inert vehicle (petrolatum). The arm that receives treatment versus control will be determined randomly for each subject. The subject will be truthfully informed at the time of application as to which arm has received which treatment. Both sites will then be covered with a bandage and the subject will be instructed not to remove the covering until 48 hours have passed and to return to the office 72 hours after treatment so that the test sites can be read for reaction.

At the reaction reading visit, the reaction will be scored categorically based on the presence of (itching or discomfort), erythema, papules, or vesicles. If a reaction is noted, the subject will be given therapeutic treatment and will be asked to return in 6 weeks for a second treatment.

2nd Treatment: Subjects who have a positive reaction to the allergen in the first treatment will be eligible for the second treatment. The second treatment will be run exactly as the first with the exception that the subject will be told that at least one arm will receive active allergen. In fact, one arm will be treated with placebo and one with allergen. The arm that receives treatment versus control will be determined randomly for each subject. Both researcher and subject will be blinded to the actual identities of which arm is receiving placebo vs. allergen.

Also determined randomly will be the establishment of subject expectancy. The actual information that the subject and researcher will be given at the time of application regarding which arm has received which treatment will be determined randomly and independently of the actual treatment given. The true treatment information will be withheld from both subject and researcher until completion of the study.

The subject will be read for reaction and scored in the same way as in treatment one. Again, therapeutic treatment will be given as needed following the reading.

3rd Treatment: All subjects participating in the second treatment will be encouraged to return in 6 weeks for a third treatment, in which both arms will be treated with placebo only. The subject in this trial will again be given expectancy of allergen on one arm and of placebo on the other (L vs. R determined randomly).

Scoring will be according to the same standards as before, and any reaction observed will be treated therapeutically. Following the third treatment, the subjects will be debriefed and the details of the study as relate to the subject will be disclosed. Any

remaining payment for participation will be made to the subject (bringing the total to $60).

F. **Economic Considerations:** Subjects will be paid $20 for each reaction reading visit to cover expenses for travel and parking.

III. HUMAN SUBJECTS

A. **Subject population:** Adult patients recording a positive test for nickel allergy in the last 3 years at the Dermatology Clinic in the Yale Physicians Building and with no known immune or psychotic disorders or other serious health risks including severe to life-threatening allergic reactions to nickel and not currently taking corticosteroidal medications will be eligible for the study. Of these, as homogeneous a subset as possible will be selected for invitation to participate in the study. An effort will be made to create a study population that is as similar as possible to that used in the Ikemi and Nakagawa study, with the exception that no minors will be used as study subjects. Men and women between the ages of 18 and 25 will be the first subjects invited since they are the most similar, ethically-sound (minors excluded) subject population to that used in the Japanese study. The subject pool will be supplemented with the addition of older patients as needed.

• *Inclusion Criteria*

Documented nickel allergy
Over age 18

• *Exclusion Criteria*

History of severe to life-threatening allergic reactions to nickel
History of immune disorders
History of psychotic disorders
History of other serious health risks
Currently taking corticosteroidal medications

B. **Risks:** Effects of the treatment are almost always limited to local dermatitis. The local reaction usually resolves itself within about seven days, and virtually always within thirty days. There are other, very rare, side effects including triggering of ectopic flares of dermatitis from previous reactions and hyperpigmentation.

There is a minimal emotional and/or psychological risk involved with the subject's transition from not knowing the true treatment to being debriefed.

C. **Consent procedures:** Prior to subject participation, informed consent will be given as described on the consent form included with this request for approval. Subjects will be fully informed as to the procedures required in the study, as well as the potential risks and discomforts. Subjects will be invited to ask any questions they may have about the nickel allergen or placebo treatment, and will be required to give written consent prior to the first administration of treatment.

Upon completion of the study, subjects will be debriefed and given full information regarding the true identity of the applications they actually received and any questions they have about the goals of the study will be addressed.

D. **Protection of subjects:** Subjects will each be coded with a unique and randomly assigned number and set of initials. All future references to the subject data will refer to number or coded initials only. The subjects' identities will be regarded as confidential and no names or other identifying information will be disclosed without prior written consent.

E. **Potential benefits:** Participation in this study will not provide any benefits directly to the subjects. Depending on individual results, some subjects may learn something about the nature of his or her own allergy and the relationship between psychological expectancy and allergic response. The information obtained through this study, however, may help to create a clearer picture of the ways in which placebos relate to the field of allergy treatment.

F. **The risk-benefit ratio:** The very small and well-controlled risks imposed by the treatments in this study represent a small factor compared to the benefits to be gained by reaching a higher understanding of the scope and power of placebos relating to allergy and possibly to the treatment and/or prevention of allergic reactions in the future.

APPENDIX 2 – Informed Consent Form

NAME:

HOSPITAL UNIT NUMBER:

ADDRESSOGRAPH:

IV. CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE - YALE-NEW HAVEN HOSPITAL

Title of Project: Allergic contact dermatitis to sham allergen vs. nickel sulfate in nickel-sensitive subjects.

Invitation to Participate and Description of Project:

You are invited to be a subject in a study of nickel allergy using a standardized nickel sulfate preparation used to test for nickel allergy. A placebo (petroleum jelly) or "sham allergen" will also be given to some subjects. You have been chosen for this study because you have an established allergy to nickel.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed judgment. This consent form gives you detailed information about the research study which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures and possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

In this study each subject will be treated with the nickel containing gel and/or the placebo. We will decide what test substance you will receive by random selection. This

means that your testing will be decided by the luck of the draw and not selected deliberately because of any specific characteristics or problems you have.

An important element of this study is the withholding of information regarding the identity of your test (allergen or placebo) until the conclusion of the study. After the first office visit, neither you nor the person applying your test will know whether you are receiving allergen or placebo. Though neither you nor the investigator will know for sure which preparation(s) you have received until the end of the study, the investigator will be given some information regarding the identity of your test preparation(s) at various stages of the study. This information may be true or false; in fact, it will be determined entirely by chance. He or she will be encouraged to share this information with you at the time the test is applied.

The study will be conducted at the Yale Dermatology Clinic, located on the 4th floor of the Yale Physicians Building, 800 Howard Avenue and at Hope Building at the Yale School of Medicine, 333 Cedar Street. It will last for approximately 16 weeks. At the first office visit you will be given a test on each arm, which will then be covered with a small bandage. You will be told which arm has received allergen and which has received placebo. You will be expected to leave the test patches undisturbed for 2 days. You should remove the bandage and test chamber 48 hours after you leave the office. After removing the bandage and test chamber, be sure to keep the test site dry. If you experience intense itching or severe discomfort before the full 48 hours have passed, you may remove the test patch causing the discomfort. You will need to return to the office 3 days after you receive the test patches (1 day after you remove them) to have your test site read for the presence of a reaction. If you develop a reaction you will be given treatment at no charge to help the reaction to subside.

You will be asked to return to the office in 6 weeks for a second test which will be very similar to the first. For this test, however, the information you are given regarding the identity of the application to each arm will be determined by chance. As with the first test, you will be expected to leave the test patches undisturbed for 2 days. You should remove the bandage and test chamber 48 hours after you leave the office. After removing the bandage and test chamber, be sure to keep the test site dry. If you experience intense itching or severe discomfort before the full 48 hours have passed, you may remove the test patch causing the discomfort. You will need to return to the office 3 days after the second test also, to have your reaction read and to be given therapeutic treatment if necessary.

The third and final test will be done 6 weeks after the second treatment, with the same procedure and follow-up described for test 2 above. You will be expected to leave the test patches undisturbed for 2 days. You should remove the bandage and test chamber 48 hours after you leave the office. After removing the bandage and test chamber, be sure to keep the test site dry. If you experience intense itching or severe discomfort before the full 48 hours have passed, you may remove the test patch causing the discomfort. At the third and final follow-up visit, you will have an opportunity to ask questions about the true identity of the test substances you received over the course of the study.

Risks and Inconveniences

Topical exposure to nickel sulfate can cause dermatitis, or rash-like skin symptoms, in allergic individuals. In only very rare instances, nickel sulfate can cause existing or preexisting dermatitis to flare up again, and can also cause skin darkening in some individuals.

A placebo is an inactive substance (for example, a sugar pill) which looks like other pills but has no medical effects. In this study the placebo, or sham allergen, will be petroleum jelly, which looks, smells and feels very much like the active treatment (nickel sulfate-containing jelly) and cannot be distinguished from it except by laboratory analysis. For the purposes of this study, petroleum jelly has no medical effects.

Benefits

This study will be of no direct benefit to you but may improve our knowledge of how to treat patients with nickel allergy.

Economic Consideration

You will be paid $20 for each test up to a total of $60 for the entire study to help defray the cost of travel and parking. Payments will be made at each follow-up visit where you return to the office to have your test reaction read. The office visits and test treatments, as well as any therapeutic treatment required to resolve a reaction will be provided free of charge.

Confidentiality

In all records of the study you will be identified by a number and/or a fake set of initials assigned to you. Your real name and any other identifying information will be known only to the researchers. Your name will not be used in any scientific reports of the study without your written consent.

In Case of Injury

If you develop dermatitis or any unanticipated side effects of the treatments you receive, we will treat you at no charge. You or your insurance carrier will be expected to pay the costs of treatment of injuries not mentioned in this paragraph. No additional financial compensation for injury is available.

Voluntary Participation

You are free to choose not to participate and if you do become a subject you are free to withdraw from this study at any time during its course. If you choose not to participate or if you withdraw it will not adversely affect your relationship with the doctors, this office, or this hospital.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully --as long as you feel is necessary -- before you make a decision.

SUMMARY

A study of patients with nickel allergy

Risks of drugs and procedures

Nickel sulfate jelly - standard nickel allergy test substance, can cause dermatitis

Petroleum jelly - inactive substance, the sham treatment
Assignment by chance
16 week duration, 6 office visits total

$60 total payment to defray costs of participation in study.
Free treatment as needed.

Authorization

I have read this form and decided that _____ will participate in the
(name of subject)
project described above. Its general purposes, the particulars of involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Signature: _____

Date: _____

_____ _____
Signature of Primary Investigator Phone

or

_____ _____
Signature of Person Obtaining Consent Phone

If you have further questions about this project or if you have a research related injury, please contact the principal investigator, Daniel Kline at (203) 787-7128.

If you have questions about your rights as a research subject, please call the Yale Human Investigation Committee at (203) 785-4688.

THIS FORM IS VALID ONLY UNTIL: _____
HIC PROTOCOL #: _____
INITIALED: _____

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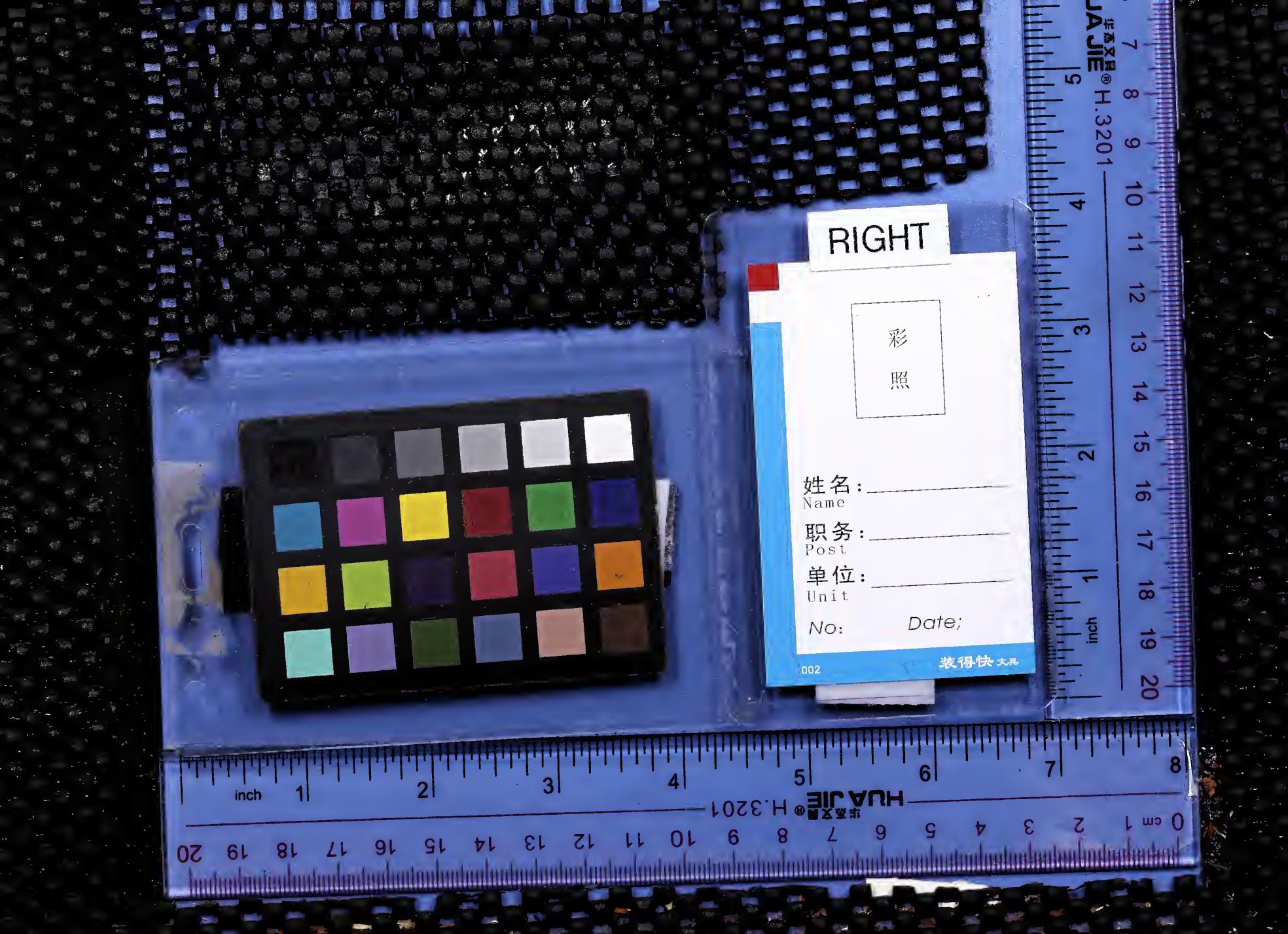
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