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Psychological effects of sublingual allergy testing : a double-blind evaluation.

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PSYCHOLOGICAL EFFECTS OF SUBLINGUAL ALLERGY TESTING: A DOUBLE-BLIND EVALUATION

A Dissertation Presented

By

DAVID S. KING

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A B S T R A C T

Psychological Effects of Sublingual Allergy Testing: A Double-Blind Evaluation

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Clinical ecologists theorize that exposure to allergens can result in cognitive and emotional symptoms as well as physical symptoms in susceptible individuals. A literature review found that research either directly supports the theory, but is poorly controlled, or is well-controlled but only indirectly supports the theory. The present experiment was a double-blind evaluation of the psychological effects of sublingual allergy testing. It was hypothesized that greater psychological changes would occur on allergen trials than placebo trials, and that greater changes would occur on placebos than base rate trials. Subjects were 20 female and 10 male patients at the Alan M. Mandell Center for Bio-Ecologic Disease, who were selected for research because they complained of at least one psychological symptom. Self-report, heart rate and a variety of mood

and performance measures were obtained in a repeated measures design incorporating base rate, placebo and allergen conditions. Scores on the MMPI, Social Acquiescence Scale, and the Health Locus of Control Scale were also obtained.

MMPI scores indicated a pathological population. Social Acquiescence was lower than in a standard sample ($p < .001$). Health Locus of Control scores did not differ from a normal sample. Expectations were not generally related to self-report symptoms. Cognitive-emotional symptoms were found to occur significantly more for allergens than for placebos ($p < .002$). The placebo cognitive-emotional symptoms did not differ from base rate. These symptoms in the allergen condition included many that could be classified as psychiatric. Mixed self-report symptoms occurred more to allergens than to placebos ($p = .011$) and placebos produced more of these symptoms than occurred in the base rate ($p < .05$). Somatic symptoms were significant over trials ($p < .05$), but not over subjects. Again, placebo somatic symptoms occurred more than in the base rate ($p < .05$). Severe reactions requiring relief occurred only on allergen trials when doubtful occasions were removed ($p = .002$). Heart rate change did not vary according to condition, but greater variability of change was found for the allergen condition ($p = .004$) than for the placebo condition. Other dependent measures were not affected by the allergens or by the placebo, and thus are not informative in explaining clinical symptoms. Implications of these findings for psychology and medicine are discussed.

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CHAPTER I

INTRODUCTION

> One man's meat is another man's poison.
> --Hippocrates
>
> ' . . . it appears to me necessary to every physician to be skilled in nature, and to strive to know, if he would wish to perform his duties, what man is in relation to the articles of food and drink, and to his other occupations, and what are the effects of each of them to every one.' (Hippocrates, quoted in Dickey, L., 1976c, p. 26)

Such concern over individualized reactions to exposures to particular dietary and environmental agents may have been an early recognition of allergy as a cause of distress. Throughout history, anecdotal accounts of severe reactions in certain individuals upon exposure to apparently harmless substances have accumulated. No systematic scientific study of the phenomena took place until the early 1900's, when the term anaphylaxis was coined to describe an apparent loss of protection of prophylaxis in laboratory animals upon repeated injections of foreign protein (Speer, 1970d). This reaction of the central nervous system often led to collapse and death (Philpott, 1974). It was later found that the term was a misnomer, since protection was not lost, but a sensitivity was acquired. In 1906, von

Pirquet introduced the term allergy to describe an altered reaction to tuberculin, a name which was appropriate for reactions of lesser severity than anaphylaxis (Speer, 1970d). Such disorders as asthma, hay fever, urticaria and others were soon placed under the allergy rubric (Leigh & Marley, 1967).

Randolph (1976d) has analyzed the medical development of allergy since that time in terms of the influence of endogeny, an approach emphasizing the internal or proximal causes of allergic reactions. Thus, the antigen-antibody relation was scrutinized, and allergic reactions were treated by drugs to alleviate symptoms. Opposing this trend was what Randolph calls exogeny. This approach emphasizes the environmental etiology of symptoms and attempts to alleviate symptoms by discovering and eliminating the environmental cause whenever possible. Thus, in an asthmatic patient, the endogenous approach would be to prescribe bronchodilators for symptom relief. The exogenous approach would be to use certain testing techniques to locate and minimize allergic contacts. The advantage of the endogenous approach is that it is easy to administer with minimal restrictions of the patient, but it usually fails to locate the causes of allergic illness in a given individual, and may allow reactions to become more severe over time. The advantages of the exogenous approach are the avoidance of drugs and the lessening or elimination of symptoms through dietary

and environmental control. The disadvantages of this philosophy are the time consuming nature of diagnosis and the necessary restrictions in the patient's life to avoid allergens. Superior clinical results have been claimed for the latter approach (Randolph, 1976d), but controlled evaluations are lacking.

To oppose the dominance of the endogenous, immunological framework of allergy, the exogenous field of clinical ecology has developed (Dickey, 1976a). Asserting that the undue emphasis upon antigen-antibody relationships has unjustifiably narrowed what is defined as allergy, they have noted that the original concept of allergy was of "observable altered reactions to specific environmental exposures" (Dickey, 1976b, p. 5). In this sense, a substance that may evoke no immunological response may be shown to be an allergen for an individual if it can be demonstrated to induce symptoms for that person. While most physicians minimize the role of food allergy (Dickey, 1976c), clinical ecologists have found it to play a major role in the symptoms of many patients. In addition, virtually any environmental substance which comes in contact with the body has been found capable of inducing allergic reactions, including such substances as tap water, toothpaste, deodorants, and inhalants as well as foods.

These reactions may involve virtually any organ system of the body, including the brain. Thus the lungs

are involved in allergic response in asthma, the nasal membranes in hay fever, the skin in hives and the digestive tract in stomach upset or diarrhea. In considering the widespread symptoms produced by allergy, it must be emphasized that no physician would argue that a given symptom is always allergic. Difficulty in breathing accompanied by wheezing can have non-allergic causes. Etiology must be established before one can safely label a symptom.

Clinical ecologists also differ from mainstream allergists in that they recognize not only a broader spectrum of causes of symptoms, but also a broader set of symptoms caused by allergen contact. Included in this grouping is what have been termed cerebral reactions. These allergies of the central nervous system are related to the anaphylactic reaction described above. Anecdotal accounts of such reactions are common. A writer of 1621 may have had a milk allergy leading him to prescribe that

> 'Milk and all that comes from milk increase melancholy and are not good for those who have unclear stomachs and are subject to headache' (Speer, 1970d, p. 4).

Philpott (1974) notes that in spite of their long history, fewer than 30 references exist in the allergy literature between 1902 and 1970 on the relation of allergy to behavior and emotions. More recently, the physician Walter C. Alvarez has described a severe cerebral reaction of his own, in which he had been very hungry from physical

exertion on a Friday and had eaten an entire broiled chicken. He reports:

> Next day I had severe diarrhea, and with this I became so dulled I could not read with comfort. And that night I had hallucinations of sight, such as I had never had before and haven't had since. In the evenings when I would close my eyes, I would seem to go into a strange new world with many colors. These visions came every night until Tuesday when again I was well. (Alvarez, 1970, p. ix)

In order to understand why such a cerebral reaction should occur, it is necessary to present the basic principles of allergy, according to the clinical ecologists. These principles apply to all forms of allergy, but of course include cerebral reactions.

The most influential theorist among this school is probably Randolph (1976a,b,c,d,e), who has discussed food allergy and other aspects of allergy at length in a large number of publications. Rinkel, Randolph, and Zeller (1951) define food allergy as:

> a term used in reference to those foods for which it is possible to demonstrate a cause and effect relationship between the ingestion of a specific food and the production or accentuation of allergic symptoms. This relationship must not only exhibit specificity, but it must be demonstrated repeatedly and upon every occasion when the tests are performed correctly. (p. 5)

Food allergies are of two types, cyclic and fixed. Fixed food allergies are unchanging, such as in a person who always becomes ill following the ingestion of lobster. Such a reaction is commonly accepted as allergic, since the etiology is often obvious to the person and observers. More insidious

and more common are cyclic food allergies. In these allergies, the degree of sensitivity (or, conversely, tolerance) depends primarily upon frequency of exposure and, to a lesser extent, the amount of food consumed at a time (Mandell, 1973). If an individual eats a certain food very frequently, s/he may develop an allergy to the substance. If the person avoids the food totally for a period of time, some tolerance to the food may be reacquired. The degree of food sensitivity is therefore dynamic rather than static in cyclic allergy.

To illustrate these principles, a hypothetical case is presented. Suppose a person had never consumed cow's milk in any form in his/her life. We will assume s/he possesses a high degree of tolerance to milk, although this is not always true. S/he begins consuming milk once daily. With each exposure, we assume his/her tolerance for milk is slightly lessened. When sensitivity reaches a reaction threshold, allergic symptoms in some form will follow each meal containing milk. The form of the reaction to milk will depend on the individual. It is not known if any general trends in reactions to particular foods across individuals exist.

If our subject continues to consume milk on the same schedule, s/he risks increasingly severe reactions, while avoidance of the food would usually lead to greater tolerance. A very significant development will occur, however, if s/he repeatedly consumes the milk again before

his/her allergic symptoms from the previous feeding have subsided. Over time, the milk reaction tends to shift from immediately following the meal to several hours following the last feeding. Instead of acute reactions, low grade symptoms will become chronic, which are now relieved temporarily by a feeding. Thus, our allergic subject at this stage will suffer from chronic low grade symptoms until s/he has milk, at which time s/he will feel better. S/he may even conclude that milk agrees particularly well with him/her, or that it gives him/her a "boost". This relief is followed after several hours by an accentuation of the symptoms. This stage which follows tolerance and active sensitization is known as food addiction.

The term addiction is used in exactly the same sense as in addiction to drugs, although drug addiction is often more advanced. Just as in drug addiction, the food addict needs a regular ingestion of the food to alleviate discomfort. Failure to obtain such an exposure will result in withdrawal symptoms. Such addiction is often found among alcoholics, for example. Randolph (1976b) has found addiction to one or more foods involved in the manufacture of alcoholic beverages to be so common among alcoholics that he assumes it to be present until repeated tests fail to indicate any allergy. Unfortunately, addiction to coffee often replaces alcoholic beverage addiction in these individuals.

If our food addict avoids milk in all forms and in any quantity for four full days, s/he should experience a period of withdrawal from the food. On the fifth day, re-exposure to milk will result in a hyper-acute reaction, a reaction more severe and obvious than any previous response to the same dosage. This period of avoidance (withdrawal) followed by heightened reactivity is true of drug addiction as well as food addiction (Randolph, 1976a). If avoidance is begun at the point of addiction, our subject will revert to active sensitization and then may regain relative tolerance to milk. Once allergy to a food is incurred, avoidance will lead to tolerance for most, but not all such foods. After tolerance is regained, spacing of the food in the diet is essential to maintain tolerance and thus prevent the recurrence of allergic reactions to that food. How easily a given individual shifts on this tolerance-allergy-addiction continuum is influenced by many factors, but there does seem to be a large degree of variability among people on this dimension. Allergic individuals shift very readily, while non-allergics may maintain relative tolerance their entire lives. Allergically ill individuals usually have multiple food and chemical sensitivities and addictions.

Randolph (1976c) has mathematically expressed the relation of dosage and individual susceptibility to severity of allergic reaction in the following way: $R = E \times S$. If either E (exposure) or S (degree of individual susceptibility)

is zero, no reaction can occur. If the exposure is to a massive dose (say, 100) occurring to an individual of low susceptibility to the substance (say, 5), a reaction of magnitude 500 will occur. A reaction of equal intensity will occur to an individual of high susceptibility (100) upon a minute exposure to an allergen (5). Randolph observes that the dosage in the latter case is often dismissed as so small as to be incapable of inducing a reaction. Often the subject who claims susceptibility to such small dosages is believed to be emotionally disturbed. If such a subject can successfully practice avoidance for four or more days between exposures, tolerance may accrue so that the occasional exposure will engender no symptoms. Thus, while exposure on Monday may have no effect, exposure on Tuesday or Wednesday may result in a reaction, since S has increased as tolerance decreased with insufficient spacing of contacts. When this pattern occurs fortuitously, patient, physician and friends may often be puzzled by such inconsistent reactions, and psychosomatic interpretations are easily made.

It is important to have an understanding of the minute dosages of allergens needed to induce reactions in susceptible individuals. Mandell (1973) reports that test-induced reactions to ethanol (related to ethyl alcohol) require the equivalent of 1/3000 of a drink. Some patients react to 1/75,000 of a drink.

The food allergy-addiction model has been extended

to include other environmental contacts (Randolph, 1976a), including drugs, chemical additives, and contaminants of air, water, food and drugs. The most important sources of illness are the common foods (the more frequent and larger exposures leads to a greater probability of tolerance loss), drugs and environmental chemicals.

The cycle of relief followed by later withdrawal symptoms is affected by several factors. In general, when a food is eaten only once daily, withdrawal may persist as long as twenty hours. When the addictant is consumed several times daily with 10 to 12 hours of relief following ingestion, reactions would normally occur only upon arising, with relief coming in breakfast if the food is consumed. Such a person might report that s/he must have breakfast in order to feel well. These relief cycles can be shortened by greater individual susceptibility or other factors, leading to shorter cycles of as little as thirty minutes to an hour. Such short cycles are most commonly found with tobacco, drugs, coffee, and foods or food-drug combinations (chocolate, colas, tea) which are rapidly absorbed (Randolph, 1976c).

Addictive "masking" of allergic symptoms can be uncovered by total avoidance of the food followed by test re-exposure, as noted above. The four day period is related to the length of time necessary for the food to pass through the body. Another technique that breaks through the addiction to reveal an allergic response is to consume larger or

more rapidly absorbed portions than usual (Randolph, 1976a). A person addicted to the equivalent of two slices of bread (wheat) at dinner may suffer symptoms after an unusually large dose, such as in a spaghetti dinner. The corn addict will be more likely to experience illness upon drinking bourbon (corn-derived) if s/he does not consume such beverages frequently, since alcohol speeds absorption and the allergen is more rapidly brought to bear upon tissues. Sugars are also more rapidly absorbed than other foods, and carry the allergenic activity of their source, such as cane sugar, beet sugar, or dextrose (corn).

Even if our corn addict were to become aware of a corn allergy, it would be virtually impossible to avoid corn contacts without assistance. While whole corn is easily avoided, and a careful scrutinizing of labels will provide further help, how likely is the person to know that his/her potato chips may contain corn in the form of dextrose which may have been added to the salt used on the chips? It is conceivable that corn oil was used in processing, but the label may only list vegetable oil. Common foods such as corn, wheat, or cane sugar are often added to food products and are therefore difficult to avoid.

The reaction of Alvarez should now be comprehensible if we mention that he had been in the habit of having chicken every Sunday, and had suffered from what he termed 'dumb Mondays' although he had never linked the two. His Friday

dosage was very much larger than usual, and so not surprisingly led to advanced symptoms. Alvarez reports that when he stopped eating chicken, his Monday trouble ceased (Alvarez, 1970). Obviously, this case study is offered primarily as an illustration and as support for the theory, not as proof.

To complete this brief and simplified account of the theory of allergy according to this viewpoint, one further link must be forged. This is Randolph's (1976a, 1976e, 1973) stimulatory-withdrawal theory of allergy. Speer's (1970a) allergic tension-fatigue syndrome is similar. The stimulatory-withdrawal model is far broader than conventional allergy theory concerned with immunological mechanisms and encompasses mental as well as physical manifestations of allergy. It was originally developed to explain test reactions and later came to be regarded as representative of the actual development of allergy in the patient.

Up to this point we have tended to focus on allergic symptoms of illness and withdrawal effects. While withdrawal effects are extremely important, they are only half the picture, since stimulatory effects are also common. Randolph locates a given individual on a continuum from extreme stimulation to homeostasis to extreme withdrawal. Frequently, the initial allergic response is stimulation such that the patient is active, alert and relatively symptom free. This response to exposures may persist for long

periods of time, and is likened to the alarm reaction in Selye's general adaptation syndrome (Randolph, 1976a). Since such individuals have few complaints, they are rarely seen by a physician at this stage. Continued exposure may lead to adaptation (addiction) in which withdrawals may become a nuisance. Such withdrawals would tend to be localized allergic manifestations such as hay fever, asthma, gas or throat clearing. Over time, both stimulatory and withdrawal phases can increase in severity. Randolph (1976a) has presented symptom features of different levels of stimulation-withdrawal in tabular form (Table 1). The more advanced stimulatory levels (+++ and ++++) are disruptive, but withdrawals usually predominate before these stages are reached.

In terms of mental effects, it may be noted that while (+) may be regarded as normal by the subject and his/her colleagues, tension appears at (++) and anxiety at (+++). While fatigue and perhaps mild depression appear at (--), more severe effects occur at deeper withdrawal levels. Randolph emphasizes, however, that in terms of all allergic manifestations, these levels are arbitrary and are not mutually exclusive. It is important to remember that these disturbances in mentation, according to Randolph, are <u>non-personal</u> in etiology, and can be reproduced at will in a susceptible individual through proper testing techniques. Test induced depression was observed as early as 1945

TABLE 1

PRINCIPAL CLINICAL FEATURES OF VARIOUS STIMULATORY AND WITHDRAWAL LEVELS OF ECOLOGIC DISTURBANCES

	Directions:	Start at zero (0) Read up for predominantly Stimulatory Levels Read down for predominantly Withdrawal Levels
++++	MANIC WITH OR WITHOUT CONVULSIONS	Distraught, excited, agitated, enraged and panicky. Circuitous or one-track thought, muscle twitching and jerking of extremities, convulsive seizures, and altered consciousness may develop.
+++	HYPOMANIC, TOXIC, ANXIOUS, AND EGOCENTRIC	Aggressive, loquacious, clumsy (ataxic), anxious, fearful and apprehensive; alternating chills and flushing, ravenous hunger, excessive thirst. Giggling or pathological laughter may occur.
++	HYPERACTIVE, IRRITABLE, HUNGRY, AND THIRSTY	Tense, jittery, hopped up, talkative argumentative, sensitive, overly responsive, self-centered, hungry and thirsty, flushing, sweating and chilling may occur as well as insomnia, alcoholism, and obesity.
+	STIMULATED BUT RELATIVELY SYMPTOM FREE	Active, alert, lively, responsive and enthusiastic with unimpaired ambition, energy, initiative and wit. Considerate of the views and actions of others. This usually comes to be regarded as "normal" behavior.
0	BEHAVIOR ON AN EVEN KEEL, AS IN HOMEOSTASIS	Children expect this from their parents and teachers. Parents expect this from their children. We all expect this from our associates.

TABLE 1--Continued

-	LOCALIZED ALLERGIC MANIFESTATIONS	Running or stuffy nose, clearing throat, coughing, wheezing, (asthma), itching, eczema and hives), gas, diarrhea, constipation (colitis), urgency and frequency of urination, and various eye and ear syndromes.
--	SYSTEMIC ALLERGIC REACTIONS	Tired, dopey, somnolent, mildly depressed, edematous with painful syndromes (headache, neckache, backache, neuralgia, myalgia, myositis, arthralgia, arthritis, arteritis, chest pain), and cardiovascular effects.*
---	DEPRESSIONS AND DISTURBED MENTATION	Confused, indecisive, moody, sad, sullen, withdrawn, or apathetic. Emotional instability and impaired attention, concentration, comprehension, and thought processes (aphasia, mental lapse, and blackouts).
----	SEVERE DEPRESSION WITH OR WITHOUT ALTERED CONSCIOUSNESS	Nonresponsive, lethargic, stuporous, disoriented, melancholic, incontinent, regressive thinking, paranoid orientations, delusions, hallucinations, sometimes amnesia, and finally comatose.

*Marked pulse changes or skipped beats may occur at any level.

Source: Randolph, T. (1976e), p. 159.

(Randolph, 1976e) in a deliberate feeding following a period of specific total avoidance. Originally attributed to chance, it was found that the accentuated test pattern could be induced as wished by testing. It was also noted that during avoidance, presenting withdrawal levels would initially worsen, followed by a return to base line (0). Thus a person with hay fever may become fatigued, and then gradually improve to baseline through avoidance.

The discussion so far has centered on the developmental sequence of stimulation-withdrawal in an individual. On a more short term basis, alternating syndromes may be observed during a test reaction. Stimulatory and withdrawal levels oscillate, and physical and mental symptoms may alternate. Randolph hypothesizes that, for example, asthma and psychosis may alternate within a given patient.

Speer's (1970a) tension-fatigue syndrome is in basic agreement with Randolph's model. By tension he includes overactivity and over-sensitivity, a state similar to stimulation. Allergic fatigue may accompany tension, but more commonly alternates with it. He claims virtually all highly allergic patients are subject to this condition, and that the syndrome may exist as an allergic disease apart from any other sign of allergy. Children with the syndrome are overactive, according to Speer, a trait which is found in allergic adults also. Such adults attempt to control their restlessness, but even when seated are identifiable by their

"frequent change of position, tapping fingers, explosive speech, restless feet and general inability to relax." (p. 15). Motor tension can result in tremors, speech problems, and clumsiness or incoordination. Further emotional and behavioral disturbances due to allergy within this framework are discussed by Campbell (1970a,b).

This discussion of allergy theory has been presented with a minimum of data to facilitate the condensation of a large body of writing to its essential principles and because the writers are generally physicians with little apparent training in experimental research methodology. Their findings are based primarily on clinical observations and careful case studies, with little attention to properly controlled nomothetic research. This is not to say that their observations are without value, since literally thousands of patients have been observed, tested and treated by their methods. Freud had a significant and continuing impact on psychology with a much smaller idiographic data base, but his concepts must be supported by observable, reproducible evidence just as must that of the clinical ecologists.

The difference of opinion between conventional allergists (and probably many psychologists and psychiatrists, for that matter, in regard to cerebral allergy) and the clinical ecologists can only be resolved by properly controlled research. Perhaps due to their medical training,

several clinical ecologists have claimed double-blind techniques are unnecessary since they find their clinical demonstrations so convincing (Dickey, 1976a). Skeptics are not easily persuaded by such reports. In any case, many vital questions in the field are unresolved. For example, the role of psychological and emotional factors in causing or worsening cerebral and other allergic reactions must be explored.

Before turning to an examination of the data available on allergy relevant to cerebral allergies both from the clinical ecologists' and other medical and psychological sources, it may be helpful to further clarify the distinction between conventional allergists and the clinical ecologists. Randolph discussed differences in philosophy in terms of endogeny and exogeny. To be fair to conventional allergists it must be admitted that they do attempt to locate and minimize causes of allergy to some degree as well as to administer drugs. But skin tests are the usual diagnostic tool, while clinical ecologists prefer fasting followed by deliberate feeding or sublingual tests with allergen extracts. The first option is based on Randolph's addictive model. (In the latter case, minute quantities of food extracts are placed under the tongue, and the patient reports any reaction that occurs.) The sublingual tests are more convenient and presumably work due to underdosage, a dose much smaller than that adapted to (Miller, 1972). Both techniques

have greater face validity than skin testing, although strict validation data are apparently not available on any technique. Criticism of skin testing is common among allergists and researchers, ranging from noting its controversial nature (Dekker, Barendregt, & DeVries, 1961) to claiming it is unreliable or a method of questionable diagnostic value (Freeman, et al., 1967; Speer, 1970c; Mandell, 1973; Davison, 1952; Rinkel, Randolph, & Zeller, 1951; Prigal, 1960; Newbold, Philpott, & Mandell, 1973).

Another distinction between the schools is that conventional allergists minimize the role of food allergy, while the clinical ecologists believe it can be shown to be the single largest etiological grouping for allergic illness. Finally, the conventional allergist treats only conventional allergic symptoms, while clinical ecologists believe a much broader approach is necessary. For this reason, the prolonged use of drugs to control allergies has been likened to an acknowledgement of failure to locate the cause of allergic illness (Mandell, 1974).

An attempt to examine the particular role of food allergy in allergic symptoms under controlled conditions was carried out by Van Metre, et al. (1968). A rigid food elimination diet was compared to a normal diet in a within subjects design. Eighteen perennial chronic asthmatics were selected for the study since their illness persisted despite treatment for inhaled allergens, infection, and

emotional factors. There was no a priori reason to assume food allergy was a major cause of their condition other than that all other approaches had failed. Subjects were assigned to the two diets for three weeks each in random order. The experimental diet was based on the principles of Rowe, a noted food allergist, but would not be recommended by clinical ecologists today even though certain elements are consistent with their approach. For example, foods were not rotated. Instead, patients ate food freely selected from a list of permissable foods which included potato, tomato, cane sugar, beef and other common allergenic foods. In addition, patients were not advised to avoid chemical exposures such as to gas, tobacco smoke, or auto exhaust. Chemicals, according to the clinical ecologists, are a major source of ecological reactions. No statistical analysis of the results was made, but a trend may have been found for the controls to do better overall.

According to the clinical ecologists, severe asthmatics are likely to be extremely sensitive to allergens, and may have multiple food and chemical addictions. In this light, it is of interest that the researchers report the failure of a small pilot study in which patients were switched to corn-free medication, but their asthma so worsened that all patients remained on their normal medication during the study. Corn is a frequent addictant. If the patients were addicted to the corn in their medication,

this result would be expected.

From this point, issues and data relevant to the question of whether allergies can influence moods and even play a role in mental and behavioral disturbances will be examined.

Frequency of Allergy

Leigh and Marley (1967) report an incidence of asthma in the general population of 1.5 to 2%, while Purcell and Weiss (1970) claim a rate of 2.5 to 5% depending on method of estimate. Luce (1968) found that asthma or other related allergic illness afflicts 10% of the American population. Boys were found to be asthmatic twice as often as girls, the difference disappearing in adulthood. No explanation is known for this sex discrepancy.

Dickey (1976c) reported a 1934 survey of a community in Virginia in which 10% of the villagers were found to have major allergies requiring medical attention and 50% to have minor allergies. The survey technique used was probably open to demand characteristics and other sources of error. The allergist Coca estimated that roughly 90% of the general population had at least one food allergy, while another researcher found the figure to be closer to 95% (Corwin, 1976). A single food allergy, of course, need hardly be incapacitating.

It is of interest that the literature contains little

on allergy among animals. Only one report of spontaneous rather than induced allergy was found in a cursory search of the literature. Guinea pigs were experimentally induced to produce asthma-like responses (Leigh & Marley, 1967), but this may not have been equivalent to human asthma (Philipp, Wilde, & Day, 1972; Freeman, Feingold, Schlesinger, & Gorman, 1964). Prigal (1960) reports that the presence of infection greatly eases the sensitization of the rabbit to ragweed. Knight (1976) reports research which found that the incidence of allergy among cats increased greatly depending on the proportion of cooked food in the diet. On a diet of 2/3 raw food and 1/3 cooked food, cats were apparently normal and healthy. On a diet of 2/3 cooked food and 1/3 raw food, the cats' incidence of allergy increased from 5% to 95% by the third generation; other degenerative diseases also appeared. No attempts to replicate were reported. In any case, that improper diets can play a major role in the etiology of disease is well documented (Williams, 1971; Pauling, 1968), and is consistent with the clinical ecologist emphasis on proper nutrition to prevent or ameliorate allergy (Philpott, 1976a), among other approaches.

It is difficult to establish the parameters of cerebral allergy. Undoubtedly, there will be disagreement as to the interpretation of provocative tests among different schools. Much of the evidence for cerebral allergies presently consists of case studies. One is provided in

Appendix A (Mandell, 1973). A second case study is of especial interest since it may fit well into a clinical ecology framework, although the authors are apparently not familiar with the approach (Purcell & Weiss, 1970). It is provided as Appendix B. The first case is certainly extreme, but less severe reactions are common. It should be mentioned that a neutralizing dose of an allergen is an exceedingly small dose of the substance which caused a reaction, and which tends to reverse the on-going reaction. No adequate explanation for this observation has yet been advanced, although Bell (1975a) believes the hypothalamus may be "fooled" into turning off the reaction.

The argument could be raised that even if the case of C.S. were exactly as interpreted by Mandell, we can consider her case and others like it as simple misdiagnosis. They are not really mentally disturbed, in the usual sense of the term, since the symptoms apparently have a physical basis. It must be recalled that most allergists do not treat cerebral reactions since they do not recognize them as allergies. In any case, the argument is irrelevant since a diagnosis of depression or schizophrenia is generally based on symptoms, not on cause. This procedure is necessary since cause or causes are often unclear. The clinical ecologists argue that allergy may be at least a part of the cause in some instances. We can assume that an unsuspecting allergic individual with cerebral reactions would be likely to seek

psychological treatment for his/her symptoms. It is doubtful that such an individual would be turned away, and referred to an allergist. Rosenhan (1973) illustrated how one could be treated merely by claiming symptoms occurring in the past. If a patient with known major physical allergies learns of cerebral allergies and mentions allergies as a possible contributing cause of depression to his/her therapist, the client may get the impression that the therapist believes s/he is deluded, as happened to a former student of the author.

In any case, psychotherapy itself is open to question as to efficacy (Rachman, 1971), while some evidence exists that psychoanalysis may even be detrimental to the recovery of neurotic patients as compared to no treatment (Eysenck, 1966). While these critical data may suffer from perhaps inevitable shortcomings, their demand for greater evidence for therapeutic efficacy is justified. If allergy plays a role in the illness of a proportion of these patients, psychotherapy may be inefficient with this group. It need not be totally ineffective, since even a heart patient could perhaps benefit from a personality or life style change lessening stress in his/her life. It is also possible that psychological factors may play a significant role in allergy exacerbation, a point to be discussed more fully below. In any case, the role of purely physical factors in provoking conventional allergy symptoms in at least some patients is

now well established (Spector & Farr, 1976). This does not eliminate the role of such psychological factors as suggestion and placebos in modifying allergic reactions of all types (Philipp, Wilde & Day, 1972).

Kaufman (1972) noted that allergy can simulate psychiatric diseases. Prigal (1960) and McGovern and Knight (1967) both mention the experience of an allergist who observed patients during the hay fever season and found that abnormal emotional reactions occurred coincident with the onset of pollen season and disappeared with its close. He observed marked mood changes following exposure to specific allergens, before overt physical symptoms would appear. Davison (1952) reports that in 1935 he became aware of the frequent disturbance of the nervous system in allergy patients. These disturbances appeared either with or without physical allergy, but when allergies improved cerebral symptoms likewise improved.

Weiss (1966) studied the mood states associated with asthma attacks in children at a residential hospital for asthmatic children. When an attack started, the children filled out mood scales during the customary waiting period for medication preparation. Control measures on the same children were taken within 24 hours of the attack when the child was free of asthma and medication. Overall mood factor rating changes were not presented, but 19 of 28 adjectives showed significant changes during attacks, with at

least two adjectives significantly changing on each of five mood factors: depression, aggression, anxiety, ability to concentrate, and deactivation (fatigue). All six fatigue adjectives increased during attacks. Concentration words showed significant decreases on four of five adjectives in the direction of confusion during attacks, and anxiety increased significantly on four of five adjectives during attacks. The researcher mentions two possible hypotheses to explain the results: (1) the negative effect may have precipitated an attack and (2) the moods were reactions to the attack itself. A third hypothesis is also possible, since allergy may have been responsible both for the attack and for the mood changes.

The best way to demonstrate that allergies can change emotions is to attempt this under controlled conditions. The case history of C.S. suffers from the flaws of all case studies. Mandell and Rose (1968) have attempted to demonstrate emotional reactions precipitated by allergens under double-blind conditions. A single patient was injected with equal volumes of two food extracts and normal saline as a placebo in the presence of her former psychiatrist. She reacted to both foods with physical symptoms followed by the appearance of mental ones, while for the placebo no reaction was reported by the patient or observed. As the authors note, the allergens may either have produced the emotional reactions directly or the emotional reaction

may have been a response to the physical symptoms.

In addition to other limitations, it may be argued that all the cerebral allergy data are not representative of the mentally ill population. The data on this issue are summarized below.

Newbold, Philpott and Mandell (1973) tested subjects suffering from schizophrenia, neurosis, manic depression, psychotic depression reaction, and involutional melancholia by means of sublingual tests or deliberate feeding following a four day fast. All subjects were hospitalized for their symptoms at the time of the study. Unfortunately, no placebo or base rate of symptom controls were employed. Of the 56 schizophrenics, 90% were found to be allergic, with many cerebral reactions reported. The small neurotic group (n=10) reacted with such symptoms as anxiety, depression and weakness among others. A mongoloid control did not react. The greatest frequency of reaction occurred to wheat for the schizophrenics and neurotic groups, as would be expected based on previous clinical experience for normals (Rinkel, Randolph & Zeller, 1951).

Dohen, et al. (1969) randomly assigned 102 schizophrenics newly admitted to a locked ward to one of two strict diets: either a milk and cereal free diet or one high in cereals. The median day of release for those on the milk and cereal free diet was significantly lower than for the others ($p < .01$). Because the patients were aware of their

diet and the ward staff could have known dietary assignments by observing what each patient ate, wheat gluten was secretly added to the milk and cereal free diet during a second test period. By the median day of release for the combined groups, there was no difference in release rates. The diet had no effect on non-schizophrenics, although some of this group may have been brain damaged. Other foods and chemicals could be more allergenic for this group.

In a follow-up experiment, Dohan and Grasberger (1973) essentially replicated the previous study, but used length of time until discharge from the hospital as the dependent measure. The cereal-free milk-free schizophrenics were again discharged significantly faster than the high cereal schizophrenics, while in the added gluten period, no differences were found in time to discharge.

In an interdisciplinary study, Millman, Campbell, Wright and Johnston (1976) investigated the effect of allergy treatment for two years on behavioral, psychometric and neurological scores for 8 allergic children with learning disabilities. A potentially useful study was marred, however, by the failure to obtain an untreated control group from the same population. Six of the eight parents claimed to have noticed marked improvement in the child in all areas of functioning during the study. The WISC was given every three months for a total of four administrations. They averaged only two points gain over this time period for the

verbal measure, but averaged 13.5 points gain on the WISC performance test over the same period. In the absence of a control group, these suggestive results are uninterpretable. Upon the initial neurological examination, the neurologist noted a similar pattern of results for the allergic children and the neurologically impaired. Leonard (1966) compared allergic and control children, and found several differences between the groups. The allergic children took significantly longer to complete a manual dexterity task than the controls, and were not able to hold an ice cube as long as the controls ($p < .01$). Personality measures showed them to be significantly more nervous and withdrawn than the controls.

This brief review of the direct evidence for the existence of cerebral allergies is representative of the meager data now existing. Further case studies (Mandell, 1974) and theoretical papers (Randolph, 1976c; Mandell, 1976) are available, but their inclusion would not correct the errors and omissions in the research in this field. Perhaps this research and clinical experience can best be summarized as being promising but preliminary, with future better-controlled research justified in order to replicate and test alternative interpretations of the data and to more accurately establish the frequency of cerebral allergy. Alternative interpretations would include the following: (1) observed and induced cerebral reactions are placebo caused reactions. In the sense that placebo reactions are mediated

by expectations and motivational variables (King, 1976, Appendix C), both laboratory and naturally occurring reactions could be so explained. (2) The cerebral reactions are simply a manifestation of neurosis or psychosis, which may or may not also cause physical allergy symptoms. In less severe reactions, emotions such as anxiety, anger, or depression may serve to induce allergic reactions. (3) The cerebral reaction is not true allergy, but arises from emotional reactions and concern over the externally-caused physical allergic reaction.

Since we have exhausted the direct experimental evidence, it is necessary to turn to research on physical allergy to search for support or inconsistencies. This body of evidence is generally much better controlled, but usually deals with asthma rather than cerebral allergy. Since asthma and cerebral allergy are both subsumed under Randolph's (1976a, 1976c) and Speer's models, the evidence has relevance.

Addiction

Addiction is central to Randolph's position, and it is of interest to note the incidence of drug addiction among allergic and non-allergic populations. Chessick, Kurland, Husted, and Diamond (1960) report a high rate of asthma among institutionalized narcotic addicts. The rate of asthmatic history for new admissions was 5-6% and 12.5% for

those staying over two months. Although most patients had severe asthma in childhood, 80% of the addicts reported that their asthmatic attacks stopped or became less frequent when physical dependence on heroin developed. Many of the addicts who still had occasional attacks reported relief either only from heroin or more effective relief from heroin than from anti-asthmatic medication. This puzzled the researchers, since opiates are known to depress respiration.

However, this would be no surprise to clinical ecologists if heroin addiction were viewed as another form of allergic addiction. If asthmatic symptoms were a result of withdrawal from heroin, a dose of the addictant should bring prompt (but temporary) relief of symptoms.

The similarity among psychoanalytic personality theories for manic-depressive psychoses, addiction and asthma was noted by the investigators. The asthmatic literature often contains references to cycloid temperaments (Freeman, Feingold, Schlesinger & Gorman, 1964) or cyclothymic personality among asthmatics (Leigh & Marley, 1967), but these reports are not generally accepted.

Hawkins (1958) examined hospital records to find a significantly higher rate of allergies diagnosed among alcoholics than non-alcoholics. Although consistent with the allergy-addiction hypothesis, the psychological stress of consuming exorbitant amounts of alcohol may have brought latent allergies to the fore in this group.

Dohan and Grasberger (1973) report that the schizophrenics on the cereal free, milk free diet showed the most improvement during the first week or two on the diet.

Allergy and Psychosis

Randolph (1973) has noted the alternation of asthma and psychosis in the medical literature, although in his model he acknowledges that two adjacent stages can coexist. Mandell (1976) believes that cerebral reactions can occur alone or be accompanied by traditional allergies. There are many reports in the literature on this issue (Davison, 1952), but the reviews generally agree that the issue is unresolved with contradictory evidence (Leigh & Marley, 1967; McGovern & Knight, 1967; Freeman, et al., 1964). This uncertainty is due to generally poor methodology. Nevertheless, of particular interest is an experimental study on two small samples of patients in whom asthma and psychosis alternated. Injection of an asthmatogenic drug led to minor wheezing during psychosis, but led to asthmatic attacks when not psychotic.

It may be no coincidence that the antihistamines have found their way into psychiatry as tranquilizers (Prigal, 1960) and that all the anti-psychotic tranquilizers have antihistamine effects (Newbold, Philpott & Mandell, 1973).

Allergy and Neurosis

The relation of allergy to neurotic and other psychopathological disorders is a subject of frequent concern to researchers, with research concentrating on asthmatics. It was frequently reported that some asthmatics had attacks of psychic rather than physical origin. Such asthmatics would have an attack after emotionally-relevant or psychologically stressful events, and often reacted little to skin testing. Dekker, Barendregt and DeVries (1961) argued that (1) research is conflicting as to the correlation between neurosis and degree of allergy in asthmatics, and (2) skin tests are of questionable validity, as are projective test interpretations. They used inhalation tests with skin tests, and classified subjects as non-allergic if no positive skin tests occurred or if all positive skin tests were negative on an inhalation test. The Heron Two Part Personality Inventory was used to assess neurosis. No significant difference in neuroticism scores were found for the skin test reactive and non-reactive subjects, but a significant difference was found between a normal control group and the asthmatics ($p < .01$). The asthmatics did not differ from a neurotic control group.

Aitken, Zealley and Rosenthal (1969) compared 12 asthmatic adults to six neurotics and six normals on psychometric test, clinical assessment, and pulmonary function. The normals were selected in a rather unorthodox manner,

by asking acquaintences to provide names of healthy individuals. In any case, the asthmatics did not differ from the normals on any psychometric test, nor would any be diagnosed as psychoneurotic, although mean scores for the asthmatics fell consistently on the neurotic side of normals.

Block, Harvey, Jennings and Simpson (1964) obtained allergic subjects from a children's hospital and found highly allergic children to exhibit significantly less psychopathology on projective tests than an apparently less allergic group with similar symptoms. Similar results were obtained on asthmatic and hay fever suffering children. An allergy scale, the Allergic Potential Scale (APS) was composed of several factors, including a genetic weighting of frequency of allergy in relatives, skin tests, number of types of allergy in the patient, and a count of eosinophile blood cells during allergic reactions. A mean split found a significant difference between high and low APS groups, but the probability level was not reported. The authors consistently used a level of ($p < .10$) or better throughout their report. The mothers of the asthmatic children were assessed on a personality index, with a pattern emerging for the low APS mother to exhibit significantly less adjustment ($p < .05$). The two groups were compared on several possibly confounding variables, with the researchers pronouncing the groups "similar" on the variables. No tests of significance were reported on these variables. Of interest in the results

for the 62 children was a possible difference in IQ between the groups. The high APS mean IQ was 113, with 109 being the corresponding score of the low APS group. The correlation of severity of symptoms with APS score was .24. Significance is not reported, but it is in the direction of greater severity in the high APS group.

These details are important since an alternative hypothesis is possible for these results. The researchers believe the evidence indicates that high APS children have a somatic illness with psychological problems essentially irrelevant to their illness, while low APS children may require psychological intervention. A second possibility is that the low APS children may have cerebral allergies as well as asthma. Lower IQ scores and lesser severity of physical complaints accompanied with greater severity of cerebral allergies would be consistent with this position, although not essential. Even the psychopathology of the mother could conceivably be cerebral allergy in part. Thus, since few would deny that genetic inheritance probably plays at least a part in asthma (Austen & Lichtenstein, 1973; Purcell & Weiss, 1970) it would not be surprising to find similar patterns emerging for cerebral allergies.

Freeman, et al. (1964), in reviewing the evidence on the issue of asthma and psychopathology, concluded that while asthmatics probably differed from normals, these differences may be due to the experience of chronic illness.

One study has found such results for asthmatics as compared to chronic cardiac patients. They also concluded that those with lesser evidence of immunological allergy had greater psychopathology, a finding not inconsistent with the above hypothesis, since many substances provoking cerebral reactions do not function in an antigen-antibody relationship (Dickey, 1976a).

Freeman, et al. (1967) investigated the relation of allergic reactivity to MMPI scores. Subjects were 132 women who suffered from asthma, hay fever or perennial rhinitis. Skin tests and inhalation tests were given to classify the subjects into categories based on the strength of allergic reactivity. Non-reactors were contrasted with reactors on the 12 scales used, and scored significantly higher on nine of them. These were: hypochondriasis, depression, hysteria, psychopathic deviation, paranoia, psychasthenia, schizophrenia, hypomania, and the F scale (which assesses dissatisfaction and inconsistency). Again, no clear differences between types of allergy (i.e., asthma vs. hay fever) were found. The authors correctly caution that non-reactors cannot be equated with non-allergics, since for many potentially allergenic substances, the tests used were inadequate.

A similar study by Hirt, Goldberg, and Bernstein (1968) found no relation between APS score and either a projective test or the MMPI. Thirty patients were scored on APS by a single allergist, who had treated them for years.

The researchers concluded that very little relation existed between the psychological variables and measures of somatic predisposition.

Purcell, Muser, Miklich and Dietiker (1969) observed 347 asthmatic children at a children's hospital. Analysis concentrated on rapid remitters, or children who improved rapidly upon admission to the hospital. Such rapid improvement could be due to either a change in the psychological or physical environment. High and low APS subjects within this subgroup were equal in severity of symptoms, and severity was not related to personality or parental attitude differences. High APS subjects consistently tended to score significantly more highly on psychological measures of adjustment. The mothers of the low APS remitters scored significantly higher than the high APS remitters on several subscales assessing undesirable parental attitudes. They tended to endorse punitive, authoritarian and restrictive attitudes. Since this study involved only a selected subgroup of asthmatics, it is not clear if it is relevant to cerebral allergies. If diet and the exposure to chemicals were unchanged, rapid remission would seem unlikely. It is not inconsistent to postulate the existence of several subgroups within the asthmatic population, nor that several factors are involved in the etiology of a heart attack. Heredity, diet, and psychological stress conceivably could interact in such a case. The discussion of the role of stress in allergy will

expand upon this. Resh (1970) used 30 adolescent and adult extremely severe asthmatic hospital patients. Asthmatics having symptoms of unknown origin were found to have a significantly higher overall MMPI profile, and scored higher on the depression, hysteria and hypochondriasis scales than the asthmatics responding to the allergy testing.

To summarize this body of research, if we ignore Aitken, Zealley and Rosenthal's questionable results, the weight of the evidence is that asthmatics are more neurotic as a group than normals, but this finding needs further replication. If further supported, the direction of causation must be clarified. The allergic reactivity studies consistently find that reactive subjects exhibit less psychopathology than the non-reactive subjects, with only two exceptions.

Allergy and Emotion

Emotion has often been postulated to augment or initiate allergic symptoms (McGovern & Knight, 1967; Kelly & Zeller, 1969). Purcell and Weiss (1970) theorized that emotions or affect states are more relevant as behavioral antecedents to asthma than are personality types or patterns of interpersonal relationships. Patients who report psychological precipitants to their attacks usually mention one of four effects: (1) anger, (2) excitement with pleasurable feeling, (3) anxiety or worry, and (4) depression. The

authors hypothesize that physiological concomitants of these states may trigger attacks in a portion of the asthmatic population. Behaviors attached to emotional states, such as crying or laughing, theoretically may also induce attacks through mechanical irritation.

Weiss (1968) found emotional precipitants were listed as significantly higher in importance in attacks for asthmatic females who were first born than later born females. This was interpreted as being due to different parent-child relationships. No further difference was found for males.

Purcell, Brady, Chai and Moser (1969) studied the effect of varying the asthmatic child's psychological environment while minimizing the physical change. Twenty-five chronically asthmatic children were used, and the parents gave information used to rank the frequency of emotional states preceding attacks. Those higher in frequency of emotional precursors were predicted to improve significantly more during a two week period in which the children's families left and they were cared for by a substitute parent. The hypothesis was supported on all measures of asthma. The predicted no improvement group showed improvement only on a self-report measure, with objective indices showing no change. The authors interpret this as supporting their view of emotional behaviors leading to asthma, although no index was kept of the frequency of crying, laughing or other emotional behaviors.

The relation of allergic potential and emotional precursors to asthma in 47 children was investigated by Kagan and Weiss (1976). When high and low APS children were compared on the frequency of emotional precursors, no difference was found. But when the researchers then included crying as an emotional precursor, significant differences emerged such that low APS children were found to rank them more highly on two of the three indices used in the study.

Tal and Miklich (1976) hypothesized that emotional states may in themselves induce physiological changes resulting in changes in pulmonary flow rates. Sixty chronically ill asthmatic children were given skin tests and were run in three types of sessions. Neutral sessions were followed by fear sessions in which the child was encouraged to actively imagine a fear-arousing experience. The anger sessions were analogous. The feat and anger conditions significantly decreased pulmonary flow rates while increasing heart rates, while the neutral condition did the opposite. The paradoxical increased heart rate accompanied by decreased pulmonary flow rates was suggestive of a defect in the autonomic nervous system, according to the researchers. The neutral condition results were interpreted as being due to relaxation. The researchers concluded that emotional arousal and not psychopathology per se was the psychological variable responsible for asthmatic attacks. Interestingly, 38% of the subjects were responsible for the entire effect, with

62% showing no difference during the sessions. Skin test results did not correlate with results.

Physiological Factors

Biochemical data on allergy will not be extensively reviewed here, although a good deal of research is available (Austen & Lichtenstein, 1973). Relevant physiological hypotheses and research findings will be summarized briefly.

Campbell (1970a) notes that it is a well-known fact in psychiatry that allergic responses are lessened following electroconvulsive therapy. No allergic symptoms are experienced for several weeks after the last treatment, but a rebound effect may then occur.

EEG has been the subject of much research in allergies. Leigh and Marley (1967) reviewed the evidence and concluded that EEG findings in asthmatics suggest a "relatively unstable or immature nervous system" to be found in a proportion of the asthmatics, similar to that found in neurotics or psychopathic patients. But Campbell (1970b) found numerous discrepancies in the literature, with his own work showing no change in the EEG of cerebral allergy patients following allergic challenge. Millman, et al. (1976) found "soft" neurological signs of dysfunction in allergic children before treatment, and initial EEG patterns ranged from normal to moderately abnormal. Hyperventilation appeared to increase abnormalities. In summary, reports

of abnormal EEG's in the allergic population appear with sufficient frequency to warrant further careful investigation.

Several researchers have found evidence of defects or imbalances of the autonomic nervous system (ANS) in asthmatics (Philipp, Wilde & Day, 1972; Tal & Miklich, 1976). In reviewing the literature, Kelly and Zeller (1969) suggested an improper balance of the ANS in asthmatics, while Purcell and Weiss (1970) view the disease as an "overreactivity of the respiratory apparatus" (p. 620), probably due to heredity. Von Hilsheimer (1976) viewed genetic selection as being responsible for hypersensitivity to toxins and a highly reactive immune system in allergies. Recently, Bell (1977, 1976, 1975a, 1975b, 1975c, 1974a, 1974b) has presented theoretical work on the possible mechanism connecting ecological illness to physiological events in the brain. The hypothalamus is seen as a major site for activating and deactivating allergic response, and a wealth of supporting literature is reviewed in these papers. Direct human experimental testing of her model has not been reported at this time.

Conditioning

The possible role of conditioning in the etiology of allergic episodes must be considered. A common anecdote in the literature concerns McKenzie of 1886 who presented a woman with an artificial rose, after which she developed

an asthmatic attack. Later studies on guinea pigs produced conditioned asthma-like responses (Prigal, 1960). Several studies appeared in the 1950's claiming classical conditioning of asthma. Kaufman (1972) has theorized that such reactions would occur only when an individual is near the threshold for a reaction, and that conditioning itself would not be sufficient. Peshkin has observed that "' . . . asthma has not been experimentally induced in any person who is not asthmatogenetically predisposed'" (McGovern & Knight, 1967, p. 13). Purcell and Weiss (1970) argue that the original animal studies used subjective judgements of breathing difficulties, while more objective techniques have failed to replicate the effect. In the human classical conditioning studies, only about two out of 100 subjects conditioned. The original researchers were unable to replicate even these results. Purcell and Weiss concluded that conditioning of asthma remains to be demonstrated, and even the researchers frequently cited by others to support the role of conditioning in asthma would concur with the above assessment.

In a recent investigation, Danker, Miklich, Pratt and Creer (1975) obtained results consistent with this conclusion. Two studies on small samples of asthmatics attempted to operantly condition increases in peak expiratory flow rates. No improvements were found, nor even any trends toward improvement. It should be noted that the above study concerned conditioning of asthmatic responses, while this study attempted

improvement. It is possible that while conditioning may be ineffective in causing asthmatic attacks, it may be of more use in ameliorating them.

Psychoanalytic Theory

The two most influential psychoanalytical theorists in regard to respiratory allergies are Alexander and French (Freeman, et al., 1964). They hypothesized that the asthmatic attack symbolized a suppressed cry for the mother, and that excessive unresolved dependence on the mother could result in an attack when a threat of separation occurred. Maternal rejection is also prominent in psychoanalytic writings on this topic.

Philipp, Wilde and Day (1972) criticized the theory for being developed on the basis of observations of asthmatic children so disturbed as to be in psychoanalysis. Purcell, Brady, et al. (1969) found no effect on asthmatic attack frequency during the two week period preceding parental separation, in which the child was aware of the impending separation from the mother.

Freeman, et al. (1964) in reviewing the evidence, concluded that the better controlled studies in this area were notable for their lack of findings.

Glasberg, Bromberg, Stein and Luparello (1969) compared 275 asthmatic, non-asthmatic allergic, and non-allergic chronically ill groups on a questionnaire designed to assess

psychosexual stage of development. Allergics did not differ from either group, but asthmatics differed significantly from the controls. Factor analysis was interpreted as showing male asthmatics as having "strong needs for nurturance and mothering and an intense fear of separation." One scale showed "reaction formation against orality as expressed by a general dislike of food, especially of the sweet, creamy variety." In direct contradiction, the clinical ecologists find such sweet or creamy foods as cane sugar or any sugar and milk to be among the most common sources of allergy and addiction due to their frequent consumption (Dickey, 1976a). Addiction commonly leads to cravings for foods containing the addictant.

Female asthmatics presented different results than the male asthmatic on the factor analysis, but were interpreted as also expressing oral dependency. The authors mention that the measure used is of unproven validity.

Placebo and Suggestion Effects in Allergy

Placebo and suggestion effects are potentially quite relevant to the proposed research, since the clinical ecology literature is particularly lacking in proper controls for this factor. It is therefore quite appropriate to review the role of these variables in allergic symptoms. For a thorough discussion of placebo effects in general, see Appendix C.

Miklich and Tal (1976) found suggestion of emotions led to decreased forced expiratory volumes in some asthmatic children. The change in the dependent variable was not correlated with score on the Barber Suggestibility Scale. Since the relation of emotion to asthma has been supported, this research is perhaps best viewed as demonstrating that emotion can be suggested, and that the emotion led to the respiratory changes. The authors report a case study in which suggestion induced bronchial widening and narrowing in a normal subject.

Luparello, Lyons, Bleecker and McFadden (1968) investigated the effect of an allergen placebo on airway reactivity in 40 adult asthmatics. Unfortunately, the experimental procedure was flawed, and lacked appropriate controls. Only the "allergen" placebo was given, with no similar procedure used for a neutral solution. Since subjects were taking 10 deep breaths within 30 seconds, it is possible that this procedure would cause increased airway resistance among some subjects. Apparently, no significant difference was found overall between the baseline period and the placebo allergen for the asthmatics, but a post hoc analysis showed that 19 of the 40 reacted significantly to the placebo. Due to the post hoc nature of the analysis and since the overall results were non-significant, this finding is suspect. A negative finding of interest was that for the majority of the asthmatics, the placebo had no effect.

McFadden, Luparello, Lyons and Bleecker (1969) essentially replicated the above procedure with 29 asthmatics. This time, significant changes were found on two of the three breathing indices to suggestion of bronchoconstriction. Roughly half the subjects reacted, and in a second set of observations on the same subjects, 45% reacted. All non-reactors were consistently non-reactive to suggestion, while two reactors became non-reactors on the second set of observations. A bronchodilating drug was administered to all subjects as an allergen, but the non-reactors responded with a significant brochodilating effect. No effect was observed in the reactor group, perhaps due to the effect of the suggestion and the drug cancelling each other out.

Spector, Luparello, et al. (1976) compared the response of nine asthmatics to drug and placebo administration. Proper inhalation controls for the placebo were included, and responses were assessed on six physiological indices of pulmonary functioning. The bronchoconstricting drug caused significant changes on all indices, while the placebo with bronchoconstricting suggestion produced significant changes on two of the six indices as compared to the neutral inhalation control. Measures of large airways were affected, while peripheral airways were not affected, leading the authors to postulate the vagus nerve as the mediator between the suggestion and the pulmonary effect. Both reactors and non-reactors were again present.

Research into the relation of placebos and relaxation training on the respiratory functioning of 20 asthmatics was conducted by Philipp, Wilde and Day (1972). On the basis of skin test reactivity, subjects were classified as extrinsic (react to skin tests) or intrinsics (no reaction to skin tests). Subjects were given a bronchoconstricting drug or a neutral solution and were either informed correctly or misinformed as to its identity. There was no significant difference between the trials on which subjects were told the placebo was a neutral substance and when they were told it was a bronchoconstrictor. There was a trend for intrinsics to react more than extrinsics. Subjects were found to react significantly more to the drug when told it was a neutral solution than to the neutral solution when told it was a drug. This finding indicates that physiological mechanisms were more influential than psychological set. No difference was found between being told the drug was present as compared to being told it was absent when subjects were given a bronchoconstrictor, again supporting the above interpretation. In general, suggestion had no effect on the extrinsics when the drug was absent. Although relaxation improved respiratory performance, relaxation subjects did not differ from their control group on a placebo trial with a bronchoconstricting suggestion.

To summarize these results, it appears that placebos may cause a change in pulmonary functioning in some subjects,

perhaps subjects who do not react to skin testing. Even this finding of placebo reactivity among some subjects is challenged by Philipp, Wilde and Day, in the best controlled study of the group. However, their negative results may have reflected the particular dependent measure used (Spector, Luparello, et al., 1976).

All studies have found a significant proportion of asthmatics, perhaps skin reactors, who do not react in any way to placebos or suggestion. The grouping of asthmatics into placebo reactors and non-reactors could reflect differences in types of asthma, one purely physical and little influenced by psychological factors and one influenced by placebos and other psychological factors. The proportion of asthmatics reacting to the placebo, incidentally, is similar to the percentage reacting to placebos for a wide range of ailments—about 1/3 (Appendix C).

A second possible explanation for the placebo reactors and non-reactors is in terms of expectations and motivational state as explained in Appendix C. If the subjects differed in these variables, but had a common disease etiology, differences in placebo responsiveness would be predicted. Either case is consistent with the placebo model presented.

The relevance of this discussion to the proposed research is in terms of sublingual testing for primarily mental and secondarily physical symptoms. Since clinical ecologists commonly test with no placebo control, it is

important to minimize the role of suggestion or placebo factors in research.

Randolph (1976e) has argued that suggestion plays little role in test results since acute reactions have been induced by intubation exposures, and sham feedings accompanied by positive suggestion have resulted in no effect. No data are presented, however. He adds:

> As far as suggestion is concerned, chronically reacting patients are more apt to be negative to suggestion than acceptable to some new interpretation of their illnesses which might infringe upon their freedom. Even though a person may be intensely interested in learning the inciting causes of his symptoms, he is usually loath to accept an avoidance program as detailed as that associated with the elimination of corn, wheat, milk, egg, or chemically contaminated foods, or as expensive as that entailed in the reengineering of his home. Indeed, full acceptance of these cause and effect interpretations generally comes only after repeated demonstrations in which circumstances permit no alternative interpretations. (Randolph, 1976f, p. 82)

Philpott (1976a) essentially agrees, and notes no appreciable differences between blind sublingual tests and deliberate feeding tests. Addicting foods are often craved by the patient, and his/her motivation is clearly to not react to his/her favorite food. Such arguments are reasonable, but must be tested and confirmed to confer general acceptance.

A special problem with cerebral reactions is that they are subjective. Subjective reactions such as pain or anxiety have been found especially amenable to placebo amelioration, although placebo induction may be more difficult (Sternbach, 1966). It may be expected, then, that

neutralizing doses would be more prone to placebo effects than would the tests themselves.

Stress and Allergy

Many examples can be found in the literature that would seem to support the role of psychological stress as affecting adversely allergic reactions. McGovern and Knight (1967) and Kaufman (1972) provide case studies to support such an interpretation. Zamm (1976) discusses so-called psychogenic hives, but argues that asymptomatic allergic processes are already present, as in food allergy. The psychological stress is merely the final straw, sufficient to overburden the individual and produce a reaction. Treating the underlying allergy will result in no further reaction to psychological stresses.

Selye (1973, 1956) has defined stress broadly, based on his research with non-specific responses to physical and psychological stimuli. He has found that all stressor agents have an "increased demand on the body to readjust itself", and it is immaterial whether the agent or situation faced is pleasant or unpleasant, physical or psychological. They all produce the same demand for readjustment. Thus, cold, drugs, sorrow and joy all engender the identical biochemical response. If such a view of stress is appropriate for allergies, then either physical or psychological stressors would be likely to increase the risk of allergic reaction.

Weiss, et al. (1976) found viewing a stressful movie of asthma attacks led to increased difficulty in breathing for about half of the asthmatic sample. Pilot work found normals to react in a similar way to the movie. Randolph (1976a) notes that the total load of environmental exposures is crucial in determining whether an individual can adapt or maladapts with chronic symptoms. On a biochemical level, it has been argued that chronic stress depletes bodily enzyme stores (Philpott, 1976b).

McGovern and Knight (1967) review evidence supporting differences in alarm reactions between allergics and non-allergic subjects to overheating. Allergic individuals will tend to over-react to normal and sub-normal stimuli (Philpott, 1976b).

This stress-related exacerbation of symptoms is not restricted to allergies, since even psychological stress alone can make any disease worse (Prigal, 1960). In terms of mental illness, an inability to handle stress is common in psychiatric disorders (Barchas, et al., 1971).

If stress can worsen allergies, it is possible that stress reduction alone may increase the likelihood of the body returning to homeostasis (von Hilsheimer, 1976), and then become better able to deal with allergen contacts. This may be an explanation of the findings of Purcell, Brady, et al. (1969) and Tal and Miklich (1976). White (1961) found hypnosis, presumably relaxing, ineffective

for improving respiratory function in asthmatic patients. But more impressive results were obtained by Maher-Loughnan (1970) who employed prolonged hypnotic and auto-hypnotic tension relieving techniques to ameliorate asthmatic symptoms.

Relaxation training through desensitization has been reported effective for one woman apparently frightened of her asthmatic symptoms (Sergeant & Yorkston, 1969). In view of these findings, it would seem reasonable that such an effective stress-reducing technique as meditation (Wallace & Benson, 1972) should be helpful in lessening the stress load of at least a portion of the allergic population. No research on this possibility has yet been reported.

Conclusions

The discussion of stress completes the review of theory and research on allergy, and a summary with conclusions would be in order. The theory of the clinical ecologists of allergic causation of multiple and sometimes severe cerebral changes is consistent with the research findings on allergy and psychological variables, although most researchers do not even mention the possibility of this hypothesis accounting for the data obtained. That this seemingly obvious possibility of allergy causing or aggravating either psychological (cerebral) or physical (somatic) functioning has been almost universally overlooked in the

research literature is indeed puzzling. A striking example is Weiss's (1966) finding that mood changes were associated with asthmatic attacks in children, a correlation which admits three basic possibilities in terms of causation. The mood change might cause an asthma attack (psychological etiology), the attack may cause secondary emotional changes in the child, or both mood changes and the asthma attack may be due to a third variable, such as common allergic causation. Logic dictates that all three interpretations are possible until ruled out by research results, yet the final possibility is not usually considered. Presumably this apparent bias is due to a belief that the brain or at least psychological functioning is immune to allergic insult, a belief that Randolph's theory and clinical evidence presented above directly question.

It is unfortunately true that the data of the clinical ecologists testing and supporting Randolph's theory, although often dramatic and usually encouraging, are often limited by a case study methodology and by the lack of proper controls. The argument raised by some clinical ecologists that controls such as double-blind designs are unnecessary since clinical testing is so convincing to the observer quite properly will not convince the vast majority of readers, since a newly-discovered phenomenon must be scrutinized carefully before "insignificant" factors can be ruled out.

The findings of improvement in schizophrenics

following dietary restrictions (Dohan & Grasberger, 1973; Dohan, et al., 1969) are a notable exception to the above objection. While supporting the above theory, such striking findings are limited to a certain population and to a certain type of allergen (grains and milk), and do not test many other aspects of Randolph's theory. While the rest of the reasonably well-controlled experimental literature is generally consistent with Randolph's theory, these indirect findings merely support and do not rule out alternative explanations.

Hypotheses

In view of these unresolved issues, it would be quite appropriate to examine the role of allergens in inducing psychological changes under well-controlled circumstances, and over a fairly large sample of people. The central research question to be asked is whether allergen exposure is capable of affecting, directly or indirectly, a wide range of psychological functions. The null hypothesis, and the hypothesis undoubtedly held by the vast majority of allergists and psychologists, is that allergen contact can not affect these psychological functions.

In the experiment to be detailed below, patients at an allergy clinic were asked to participate in sublingual allergy testing under controlled conditions. Such controls included periods to assess the spontaneous frequency of

symptoms (base rate) as well as placebo and allergen effects under double-blind conditions. Dependent measures consisted of many cognitive tasks and other psychological tests, while heart rate was included as a physical index of allergic reaction.

Psychological measures incorporated into this study were chosen to fit two criteria: (1) they must be ambiguous to the patient in terms of how well s/he did, since it is not desirable to frustrate those who are ill; and (2) they must be very rapid measures since meaningful test reactions may at times be fleeting.

A secondary portion of the experiment was the administration of several trait measures, such as the MMPI, to give an index of how the patient population at the clinic compares to asthmatics on these measures in the literature. Secondary analyses were also possible, such as relating depressive reactions during testing to the score on the depression scale of the MMPI.

Simply put, the major hypothesis of this study was that allergen trials would result in greater change on the dependent measures than the placebo trials. A secondary question concerned the role of placebos in allergy responsivity, especially in regard to cerebral functions. While placebos are ineffective with asthmatic skin-reactors on pulmonary functioning, they may or may not be effective for psychological allergic reactions. No prediction can

reasonably be made since data is lacking on this point, although the clinical ecologists claim suggestion plays no significant role in allergic reactions. On the other hand, numerous psychological reactions have been reported to pill placebos (King, 1976, Appendix C), but these have inevitably been confounded with possible allergic reactions.

It was further hypothesized that allergic responses on the initial trial for each allergen will not be correlated with a measure of expectation, or at least will be less correlated than the placebo responses. For similar reasons, a measure of social acquiescence should correlate less with allergen response than placebo response.

It was hypothesized that a correlation will exist between heart rate and severity of allergic reaction. This correlation is not expected to be extremely high, since clinical observation finds only a moderate relationship. Heart rate change should be greater in the allergy trials than the placebo trials.

C H A P T E R I I

METHOD

Subjects

Subjects were 30 adult patients at the Alan Mandell Center for Bio-Ecologic Disease in Norwalk, Connecticut. These patients came to the clinic for a variety of reasons and through a variety of sources. Some patients suffered from conventional allergies such as hay fever and asthma, while others had diffuse, vague or psychological symptoms. They were sent by other physicians or came by self-referral based upon popular accounts of Dr. Mandell's work. Probably a little less than half had psychological symptoms reported as a presenting complaint. Reluctance to mention such symptoms and instead to focus on a more "acceptable" symptom may hide some patients with psychological symptoms. Subjects for this experiment were selected on the basis of having at least one psychological or mental presenting symptom, such as anxiety, depression, confusion, or difficulty in concentrating. At least two-thirds of the subjects who were requested to participate, agreed. Of those who refused, many claimed time constraints or similar reasons for declining. One potential subject was too confused to understand what

was requested of her. Of the subjects who agreed, several mentioned that if they could help even one person to not go through what they had to go through by doing the research, they would be happy to participate. By this means, 20 female and 10 male subjects were obtained, ranging in age from 17-56. The difference in sex ratio is probably affected by housewives being more easily available for days of testing than working men. Students were also common. No data was obtained on income levels, but the distribution appears biased toward the middle and upper classes. Patients were asked to participate voluntarily, for purposes of furthering knowledge of allergic disorders and to obtain more information on themselves that could be useful to the physician.

The experimenter was a 27 year old male, dressed professionally, who was described as a researcher working with Dr. Mandell. He has had some clinical psychology training.

Materials

Sublingual testing materials were provided by the clinic, since the allergy tests were necessary for proper diagnosis, whether for research or in normal testing. Standard sublingual allergenic extracts were used in the three different dilutions normally used in the clinic. The allergen materials used in this study consisted mainly of foods and tobacco smoke, although occasionally a chemical

test was used. These tests were chosen on the basis of the individual's frequency of exposure. The most common tests included wheat, cane sugar, milk, beef, and tobacco smoke. The placebo material was triple-distilled water, chosen to minimize the possibility of a biological reaction to the placebo itself.

The research testing was conducted in a small room, roughly 4' by 6', located adjacent to the main testing room at the clinic. A sliding door dampened noise from the testing area, and was closed except when the summer heat necessitated greater ventilation. The only window opened onto the clinic parking lot above and due to the season, it was often open to allow air in as well as exhaust fumes. The subject and the experimenter each had a chair with a writing arm, and were seated across from one another.

The experimental substances (allergens, distilled water) were administered in the standard way, via syringes used to squirt the measured dose under the subject's tongue. A total of 21 syringes were used for each subject, and because this was a double-blind design, the allergens and placebos were prepared and disguised by one of several assistants at the clinic. Cigarette rolling papers and rubber bands were used to hide the color of the solution in the syringe from view, with the identity of the substance on a label under the paper. This code was broken after each subject completed the tests, and the order was recorded.

The dependent measures are listed in Table 2, and the rationale for the inclusion of each is discussed below.

TABLE 2

DEPENDENT MEASURES

Heart rate
Signature, 1-10
Bender-Gestalt
Digit Symbol Substitution
Block Design
Cancellation
Uses of
Time Estimation
Mood check list
Graphic constriction-expansion
Self-report
Relief requests

Heart rate, for example, is reported to bear a moderate relationship to allergic reactions (Dickey, 1976a). It potentially provides a physical index of allergic reaction, and was assessed by means of a San-Ei Pulsemeter Model 2D16 with a finger plethysmograph. The pulsemeter was placed on the experimenter's desk facing away from the subject so that it would be difficult or impossible for the subject to view the dial.

A second dependent measure was the subject's own signature and writing of the digits 1 to 10. This is an over-learned skill, with no practice effects likely. Psychomotor or coordination decrements were expected to be revealed by this quick measure. Signature size may also reflect self-esteem, which might vary during testing due to reactions (Zweigenhaft & Marlowe, 1973).

The Bender-Gestalt test is a recognized and respected test of organic brain deficit. It was thought possible that the functional impairment of allergic cerebral reactions may also be assessed on this task. Only one card was used per trial, with no time limit on completing the drawing. The order of presentation of the cards was the same for all subjects, since the appearance of the placebos was randomized independently for each subject.

The WAIS Digit Symbol Substitution test is highly correlated with the overall WAIS score (r=.71), and so is useful in intellectual assessment. Confusion, psychomotor impairment, fatigue and other factors may impair performance during allergy testing. Four parallel forms of the test are available (Yeats, 1974). One minute was allowed for this test, which was given on the first three allergen/placebo substances. The rationale for the WAIS Block Design test is similar to that for the Digit Symbol test. One different card was used for each of three trials when the Digit Symbol Substitution test was not presented (D, E, and F). In other words, the Digit Symbol Substitution test was given on the first three allergen/placebo trials, and a Block Design card was given on the last three trials.

The Mood Affect Adjective Check List (MAACL) short form is a rapid, convenient means of assessing anxiety, depression, and hostility; all of which are reported capable of being induced allergically (Dickey, 1976a). It was given

once for each substance.

The Graphic Constriction-Expansion test (Wallach & Gahm, 1960) consists of measuring the area covered by a subject's doodle, and is supposedly an index of the trait of the desire to be isolated, but in this study it was used as a state measure. This adaptation has been successfully used previously (Hale & Strickland, 1976; Strickland, Hale & Anderson, 1975).

The "uses of" test asks subjects to simply list uses of an object within the allotted time period. Presumably impairment of higher cognitive functioning would decrease the quantity or quality of output. Two minutes were allowed for listing the possible uses of each of the following objects: brick, coat hanger, used auto, book, match, shoe, jar, and knife. Responses were scored for fluency (raw number of responses) and flexibility (the judged number of different categories of the responses).

In the cancellation task, subjects simply crossed out digits on a page of random numbers as rapidly as they could for one minute. Subjects crossed out 2's, 5's, and 7's the first half of the experiment and 6's, 8's, and 9's the second half. Cancellation accuracy has been found to be unaffected by placebo administration (Lehman & Knight, 1960), but confusion and other cognitive impairments may hinder performance.

Self-report of reactions is an important index

since it is routinely used in clinical testing and any subtle or unusual reactions may be missed otherwise. In this study, all reported symptoms were recorded, regardless of whether they were mental or physical. Subjects also rated the severity of the change in each symptom on a 7-point scale (Appendix D).

The experimenter originally intended to record carefully any observable changes or reactions in the subject such as flushing, speech changes, or other behavioral changes. It proved to be impossible to assess and note such changes accurately for relative strangers, and at the same time to perform the administrative duties of the experimenter. For these reasons, partial records were kept and these primarily consisted of the unusual severe reaction.

In order to compare this clinical sample to other groups, three personality questionnaires were administered to the patients. These were the short form of the Minnesota Multiphasic Personality Inventory (MMPI), which assesses psychopathology; the Social Acquiescence Scale (Bass, 1956), which measures conformity and has been found to be correlated with placebo responsivity (McNair, et al., 1968; Pichot & Perse, 1968); and the Health Locus of Control Scale (Wallston, et al., 1976), which gauges the degree to which a person believes one is able to control one's own state of health. The latter two scales are brief and were usually given during the initial intake period for the patient, before testing

began. The patient was allowed to take the MMPI overnight and return it in the morning.

Expectations for a reaction to occur on a trial were assessed before each trial as shown in Appendix D. Similarly, subjects were asked to guess what the test solution was and to rate the certainty of their guess.

Procedure

The experiment was conducted from late May to the end of August, 1977. Since this field experiment was basically an addition to an existing clinical framework, the procedure was in many ways set by the standard clinic methods. During the months of May to August, 1977, patients had an initial intake interview with a staff member in which they discussed symptoms, dietary habits and their health history. At this point, if the subject fit the criterion of presenting at least one psychological complaint, they were asked by a staff member of the experimenter if they wished to participate in the research. They were told that the study would take some additional time, but that additional information about their reactions would be gathered. They might also be aiding in the understanding of allergy by participating.

If the patient agreed to participate, s/he was given a scale intended to locate possible allergens as well as the health locus of control scale and the social acquiescence

scale. Following this, the subject was scheduled for a physician consultation in which the physician questioned the individual more closely and ordered appropriate allergy tests.

Based upon the allergy questionnaire and/or the physician's notes on the consultation, the experimenter selected four allergens suspected to be the most probable to cause reactions in this patient as the allergen test substances for the patient. These four substances were passed on to an assistant to prepare for double-blind administration on the day the patient was to participate in the research. After the physician consultation, the subject may or may not have started normal allergy testing, depending on the person's schedule, time of day and the experimenter's schedule. Experimental allergens for that person were reserved, and were never given to the subject before the experiment. This procedure resulted in the chief tester at the clinic grumbling that the experimenter always got "all the good ones". So subjects were usually practiced in the testing procedure when they began the research.

Before the normal testing phase, patients were given little formal instructions other than that certain substances would be given to them painlessly under the tongue, and that they were to report any reaction or any change in how they felt. In the normal testing and in the research, when severe reactions occurred, neutralizer

doses were given to minimize or reverse the symptoms induced through testing. Other measures, such as receiving five minutes of oxygen or waiting or simply going for a walk, were also taken when appropriate. Even severe test reactions are not life-threatening (Dickey, 1976a). Most tests were given in three parts in which different doses of the allergen were given, in order to maximize the possibility of detecting the allergy, since allergic response may vary with the dose level (Miller, 1972). In this study, subjects were tested individually, with the experimenter selecting and administering the test materials as well as the dependent measures under strict double-blind conditions. When subjects were uncomfortable due to reactions, the clinic staff was called on to reverse or ameliorate reactions. It was never necessary to do this before completing the series of three doses.

An overview of the experimental procedure is provided in Table 3. There were four primary experimental conditions: (1) allergen trials, (2) base rate trials in which the subject received no substance sublingually but completed the dependent measures, (3) placebo trials, and (4) screening trials in which the subject was screened for reactions to the placebo substance itself. The placebo condition is necessary to estimate the amount of allergic response that is due to psychological causation. The base rate condition is necessary to assess the base line of

TABLE 3

EXPERIMENTAL PROCEDURE

I. Intake Interview and Questionnaire

II. Physician Consultation

III. Testing

	Screening	Base Rate	A	B	C	D	E	F	Base Rate	Screening
S_1										
.										
.										
.										
.										
.										
.										
.										
S_{30}										

responding without placebo influences such as to air pollution or foods consumed earlier in the day and to get an estimate of delayed reactions with the final base rate period. Dependent measures were identical for all conditions. Each test consisted of a series of three doses, given in sequence for the placebo and allergen trials, while the base rate and screening trials were separated as shown in Table 3. Table 4 shows the dependent variables given on each dose. Subjects were provided with a timer which they set to 10 minutes to time their own tests.

Pilot testing revealed the necessity of providing some general instructions to the patient before beginning the actual research testing process. After being seated,

TABLE 4

DEPENDENT MEASURES BY DOSE

Dose 1	Dose 2	Dose 3
Self-report	Self-report	Self-report
Signature, 1-10	Signature, 1-10	Signature, 1-10
Heart rate	Heart rate	Heart rate
Bender-Gestalt	Mood scale	Digit Symbol
Uses of	Cancellation	Block Design
Time estimation		Graphic Expansion

they read and signed an informed consent form, which mentioned the additional time involved in research, but made no hint of the fact that the extra time would be partially due to the use of placebos. They were informed that they were free to withdraw at any time from the experiment.

After this, the subjects were read the instructions to the practice sheet of the Digit Symbol Substitution test, and filled it out. The same procedure was followed for the Block Design test. They were then instructed on how to fill out the expectation sheet. After receiving a dose, they were to guess what it was, based upon its taste, and to rate the certainty of their guess. Pilot testing showed that subjects would obsess with guessing the substance (a task that is surprisingly difficult due to the minute quantity of extract used in testing), and so an instruction was added to "go on your first impression, don't spend a lot of time on it." It was then stressed that they were not to reveal in any way to me how the substance tasted, verbally or non-verbally. Because some pilot patients seemed reluctant to

mention a mental reaction, or weren't aware that a mental reaction could occur to an allergen, they were next instructed to announce when they were having a mental reaction, to be sure to mention it, and to not be embarrassed about it. They were told to announce any changes in their state, and to rate "how bad it is" on a 7-point scale from very slight to very severe.

Pilot testing revealed the necessity of modifying the actual method of administering the test substance given by syringe to the patient, because it was sometimes possible to observe the color of a test solution in the mouth of the patient. To prevent this from occurring, the wrapped-in-paper, loaded syringes were taken from the tray, and the experimenter used one hand to sight the syringe into the open mouth with raised tongue of the subject. The experimenter closed his eyes, squirted, removed the syringe, opened his eyes, and replaced the syringe in the tray while trying to avoid seeing the syringe. This procedure was found to be quite effective, except for a very few trials in which the experimenter became suspicious or knew what the substance was. These trials were analyzed separately.

Next, the procedure of wearing the finger plethysmograph to record the pulse was explained to the patient. The necessity of remaining very still during recording was emphasized. In order to get a measure of pre-experimental symptoms, the subjects were asked to mention all symptoms

they presently had or to rate their severity.

At this point, the screening trial instructions were read to the patient. Instructions were as follows:

> Now we want to practice the actual allergy testing procedure before we begin the allergy testing. You will receive a non-allergenic substance for practice. Although it is possible for a reaction to occur to this substance, it is very unlikely.

Subjects marked their expectation and then had their pulse taken three times in 90 seconds. They began screening dose 1 by receiving a squirt of triple-distilled water and setting their timer to 10 minutes. They recorded their guess as to what it was and rated their certainty. Meanwhile, the experimenter began a stopwatch after giving the squirt to allow the elapse of two minutes before placing the plethysmograph back on the subject's finger (pilot subjects found the finger plethysmograph too constrictive and hot to have on all the time, so it was placed on and off for pre-dose and for post-dose readings). At the third minute, three readings were taken at 30 second intervals, just as in the pre-dose time period. As soon as this process was completed, subjects signed their names and wrote the digits 1 to 10. They then were given brief instructions on the Bender-Gestalt test and were allowed five seconds to view the figure before it was removed and they could begin copying it from memory. Card 1 was used here, and a plain 8 1/2 x 11 sheet of paper was provided for this task. Next they turned the sheet over and were given the following

instructions for the uses of test:

> I want you to list as many different uses of a _____ as you can think of. You may use it in any way you wish. You will have two minutes to make your list. Ready? Begin.

The object this time was a brick. Lastly, they were asked to turn their timer off and to estimate a minute by saying "Stop" when they believed a minute had elapsed. They could use any means they wished to estimate the minute other than using a clock. When this was completed, subjects reported any reaction and reported its severity. Whenever a symptom was mentioned, and the subject paused as if finished, the experimenter would ask "Is there anything else?" until the subject would state that there were no more symptoms. This procedure was intended to encourage complete disclosure of symptoms, and was used for all trials. Some subjects reported symptoms as they happened, and these were recorded also, since this procedure would not affect the double-blind design and might prevent the forgetting of symptoms.

At the beginning of the second screening trial, the subject was informed that the same test would be repeated. The same sequence of dependent variables was collected until after the signature and digits were written. On this and other second dose trials, the Mood Affect Adjective Check List was administered with the instructions written on the top of the page. This was followed by the cancellation task which lasted one minute. Subjects crossed out three digits during the first half of the experiment, and three different

ones were crossed out during the second half of the experiment. They then again reported any symptoms and rated severity.

Next came the first base rate trial. Instructions were as follows:

> We need to know how well you will do on certain tests before you receive the allergy solution, in order to compare your score before and after exposure to the allergy material. So we will now have three 10 minute periods in which you will take certain tests but you won't receive any allergy material. Are there any questions?

Again, the same sequence of dependent variables was followed until after the signature was obtained. Then dose 1 variables were assessed. The Bender-Gestalt card was now #2, and the uses of test was for a coat hanger. Time estimation and self-report were as above. The second base rate period was identical to screening dose 2 in terms of dependent measures.

At this point, the allergen/placebo trials were begun. The subject was never informed that placebos were in use. Instead, they were told "OK, now let's start the allergy tests". Since almost all subjects do not expect to react to all allergy tests (otherwise, why bother testing at all?) a few trials in which the subject fails to react should not arouse any suspicion.

The first test substance for a subject could be either a suspected allergen or a placebo. Six allergen/placebo tests of three doses each were given, four allergen

and two placebo. These were labeled A, B, C, D, E, and F. The assistant used a random numbers table to randomly place one placebo test of three doses within the first three tests and to place one within the last three tests. The dependent variables for each dose is shown in Table 4. The procedure is identical to that of the screening and base rate trials for dose 1 and dose 2, except that different Bender-Gestalt cards and uses of test objects were provided. The cancellation task involved five parallel forms of random numbers. After test C, the three numbers to be cancelled were changed and the forms were repeated.

Dose 3 of test A involved the identical procedure as above until after the signature and 1 to 10 were obtained. The Digit Symbol Substitution test was given for one minute. Parallel forms were used on dose 3 for A, B, and C. On tests D, E, and F, the Block Design cards were used. These tasks were followed by the graphic constriction-expansion task, with these instructions:

> I'd like you to draw doodles on this page. Doodle in whatever way you think best expresses your mood during this test. Just draw whatever doodles you want in whatever way you want; but all your doodling should be directly inspired by your mood.
>
> One important thing: your doodles should not show any recognizable animals, people, or things in them. Don't draw people, animals, houses or anything like that. Just draw designs—whatever kind of designs your mood inspires you to draw. Your doodling should be inspired by your mood, and should be designs rather than anything specific. So now begin doodling in whatever way your mood makes you feel.

Subjects were asked to take about a minute for this

task. Following this test, self-report measures were again obtained.

The procedure outlined above was followed for all trials, based upon dose. Upon completion of F, base rate 3 was given, but dose 1 dependent measures were taken to compare to base rate period 1. On the following screening trial, dose 2 variables were taken.

If during the course of the experiment, a patient became ill or uncomfortable, steps were taken to ameliorate the reaction when the ten minute period was over. Neutralizing doses, oxygen, or just waiting for the reaction to pass were the usual means of handling this problem. If a neutralizer was necessary, an assistant had been instructed to unmask the syringe and give a neutralizer accordingly. If the last test had been beef, for example, a beef neutralizer would have been given. If it had been water, a water neutralizer was to be given unknown to the patient. The experimenter left the area at these times so as to have no clue as to the identity of the substance tested. Administering oxygen required no such precautions, of course.

When the patients completed all tests, they were debriefed and the identity of the test materials was recorded and made known to them, along with a review of their reactions. The nature of the placebo and the rationale for its inclusion were explained. They were then asked not to discuss the details of the study and especially not to mention

that placebos were in use with other patients.

It was originally hoped that all patients would begin tests early in the morning, take a lunch break after test C (the mid-point) and then finish in the afternoon. This was impossible in a good number of cases. While the sequence of tests was always preserved (there was one instance in which tests D and F were placebos due to a new assistant misunderstanding what was desired), tests were taken at different times of day, and in some cases, half were taken on one day and half on another. Whenever breaks occurred, present symptoms were again recorded.

One possible problem with the conduct of this study was that the assistant was instructed to use a random number table to randomly place the first placebo within A, B, or C, and then to do the same for D, E, and F. She interpreted this instruction to mean she was to randomly select among A, B, and C, and then place the second placebo in the corresponding position among D, E, and F. When I first noticed this consistent pattern, after 11 subjects, I immediately corrected this problem. Since neither the patients nor the experimenter was aware of this linkage, it had no effect on the double-blind design.

When all the research testing was completed, the patients were given the MMPI to take home, and then were returned to the regular testing area.

CHAPTER III

RESULTS

Judges were employed to score three of the raw dependent measures. Self-report of the over 1000 symptoms reported by the subjects were scored blind by two judges into three different categories: cognitive-emotional, mixed or somatic. Judges were provided the protocols for types (Appendix E) and were given printed sheets consisting solely of symptoms reported by the subjects, with no differentiation by experimental condition or severity. Cognitive-emotional symptoms (1's) were defined as "symptoms primarily thought of, or most likely to be, cognitive or emotional." Several examples were provided. Mixed symptoms (3's) were defined as "symptoms involving both psychological and physical factors in significant amounts or symptoms ambiguous as to whether they are physical or psychological." The somatic category (5's) included symptoms primarily thought of, or most likely to be, somatic.

Percentage agreement of the judges for the 1023 symptoms was 88%. Symptoms the judges disagreed on were placed in the category corresponding to the average value of the two judged categories, in order to average the error in judgement. For example, if a symptom was judged a

cognitive-emotional (1) symptom by one judge and a mixed (3) symptom by the other, it would be placed in a new category (2). When one judge said cognitive-emotional (1) and the other somatic (5), it was placed in the mixed category (3), which is the average of the two judgements. Logically, if one judge believes a symptom to be psychological and one somatic, it is by definition mixed.

The severity score could not be used in its raw form in the case of repeated symptoms, since the previous appearance of the symptom determined what severity to attribute to the symptom. For example, if a general headache of severity 2 was a pre-dose symptom, and on the third dose following the subject reported a general headache of severity 3, a severity score of only 1 would be attributed to that dose. If there had been no previous headache, then a full 3 point severity score would be given.

A new list of symptoms was drawn up in which symptoms were marked if they were pre-symptoms, and also divided by subject and dose. Again, the severity or experimental condition of the symptom was not provided. The same blind judges categorized each symptom as to whether it was old or new, based on preceding symptoms for that subject, including symptoms given just before the experiment began. Percentage agreement for the 824 symptoms was 86%. It would be impossible to raise the reliability much higher, since some symptoms were ambiguous on this dimension. For example, sinus

congestion as a pre-symptom was followed by frontal headache for one subject. If these refer to the same symptom, the severity score should be subtracted. If they are not, full severity credit should be provided for frontal headache. What was actually done in cases like this in which the judges disagreed was that the average of the two values (old symptom and new symptom) was taken.

In a similar manner, all experimental symptoms were scored for severity by the experimenter based upon whether the judges considered the symptom old or new. If new, the severity score was whatever the subject reported. If old, a subtraction from the previous value of the symptom was performed. The protocol for scoring self-report is provided in Appendix F. To summarize, symptom severity score was based on the subtraction from the immediately previous occasion when the symptom appeared. If this resulted in zero or a negative number, a +1 was arbitrarily assigned, since the patient must have experienced a change of at least this magnitude. If a dose resulted in spontaneous total relief from previous test provoked symptoms, full credit for the previous trial's symptoms were given since these all rapidly disappeared with the new dose. The allergy literature discusses this effect as a neutralization during testing due to the size of a dose.

Along with severity, the raw number of symptoms was also recorded. Categorization of symptoms was preserved

in this count.

The uses of test can be scored on several dimensions. The simplest is fluency, which is obtained by counting the number of responses listed by the subject. This counting was done by the experimenter. Also scored was flexibility, which is a measure of the number of different categories found in the list of responses. For example, a brick could be used for a paperweight, for a fireplace, or for construction of a patio floor. The latter two were scored as one in the building category. A new set of two blind judges scored all uses of tests for flexibility. Percentage agreement on this inherently difficult task was only 65%, but 93% of the judgements were within 1 category difference. When judges disagreed, the mean value was assigned to that trial.

The graphic constriction-expansion test was scored by counting the minimum number of squares covered on an overlaying grid by the subject's doodle. Since this was simply a counting task, an assistant and the experimenter independently scored the doodles, with a percentage agreement of 84% obtained, 96% within one unit. The discrepancy was probably due primarily to different styles in scoring borderline sections of the doodles. Again, mean scores were assigned for all trials.

Sample Characteristics

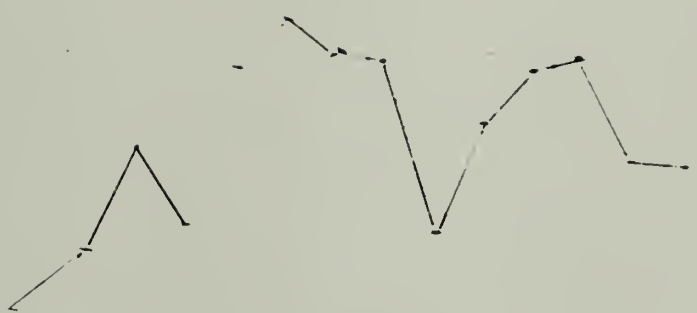
Ages of the patients ranged from 17 to 56, with a median age of 24. The MMPI, the Health Locus of Control, and the Social Acquiescence scale had been administered to the subjects to get a general index of how this non-random sample compared to known populations. The mean value of the Social Acquiescence scale, previously correlated with placebo responsivity (McNair, et al., 1968), was 19.2 in this group. The standardization mean for a sample of West Coast residents was 31.2 (Bass, 1956). The present sample was found to be significantly lower overall on social acquiescence than this group of normals on a two-tailed test ($t=4.99$, $df-76$, $p < .001$).

The sample Health Locus of Control Scale mean did not differ from a normal sample in the literature (Wallston, et al., 1976), but it was significantly more internal than a sample of hypertensive out-patients ($t=3.38$, $df=64$, $p < .002$). The latter sample confounded physical chronic illness with race, since the sample was primarily black. No psychiatric data was provided for comparison to the present sample.

Four subjects refused to fill out the MMPI. Sample mean values for the MMPI are shown in Figure 1. Standard T scores for all subjects were used to compute the mean profile. As a group, the sample evidenced pathology (above a

FIGURE 1

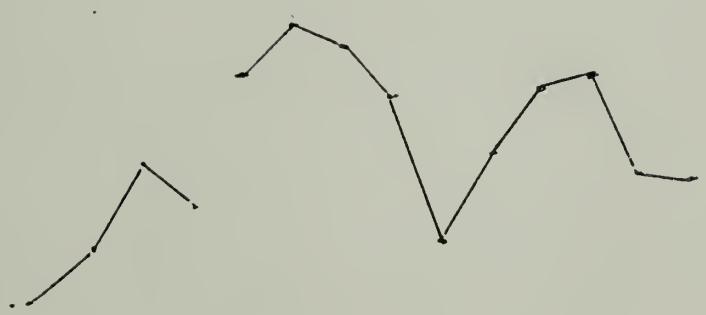
MMPI GROUP PROFILE
(N = 26)



T score of 70) on the following scales, in descending order: depression, schizophrenia, hysteria, psychasthenia, psychopathic deviate and hypochondriasis. The only scales assessing pathology, in this sample selected for psychological complaints, not above a T of 70 were manic and paranoia. Manic patients perhaps would not seek help. Five of the individual profiles were above 70 on the F scale, indicating questionable validity for these questionnaires. Their omission resulted in the profile for the remaining 21 subjects shown in Figure 2. The pattern is still the same. Only two subjects of the 26 were normal on all pathology scales. Of the valid pathological profiles, nine subjects had depression as the major symptom, six had hysteria, and the others were sprinkled among schizophrenia, hypochondriasis, and mania. No one was primarily psychopathic deviate, paranoid, or psychasthenic. In comparison, the MMPI profiles of asthmatics found by Freeman, et al. (1967) are not directly comparable because of the failure to add the K factor to scores. Even so, elevations were found on depression, hysteria, psychopathic deviate and paranoia, the last being comparatively depressed in the present sample. Jones, et al. (1976) studied 190 severe asthmatics, hospitalized for treatment. They found a strong "V" pattern on the neurotic triad (hypochondriasis, depression, and hysteria), with the highest T-score being 68 for hysteria. In contrast, the present sample had an inverse "V" pattern,

FIGURE 2

MMPI GROUP PROFILE
(F < 70, N = 21)



and had mean T-scores higher than the Jones sample on all pathology scales. The depression scale difference is the most striking. My sample excluded all serious asthmatics for safety reasons. It may be that the asthmatics were not depressed, while the depressed were not asthmatic. The greater psychopathology in the present sample is consistent with the clinical ecology theory that withdrawal symptoms may manifest themselves primarily in the form of cerebral allergies or through somatic symptoms such as asthma. The difference may be one of emphasis rather than a dichotomy.

Correlational Analysis of Subject Variables

All questionnaires and subject variables were intercorrelated. Since this is a *post hoc* procedure, a danger of spurious correlations being significant is a factor, and so weaker correlations may be viewed with caution. Since the distributions of these variables were not noticeably skewed, Pearson correlations were used throughout.

Age and sex were two subject characteristics investigated by this means. Age was found to be negatively correlated to psychopathic deviate (r=.47, p=.007) and to the manic scale (r=-.36, p=.033). No other correlation with age was significant. With men scored as one, and women as two, sex was negatively related to T score on the masculinity-femininity scale (r=.78, p=.001), and positively to hysteria (r=.61, p=.001) and hypochondriasis (r=.49,

p=.006). In other words, men in this sample had elevated T-scores on the masculinity-femininity scale (higher feminine) in relation to the women. Thus, women scored quite feminine on the scale (low T-score), and the men scored somewhat feminine also, which for them resulted in a high T-score.

Sex and age were also correlated with the dependent measure except for the measure given only a certain dose which were not significant. None of the correlations with sex were above .30, and so sex was not a major factor in those measures. The correlation was .00 for cognitive-emotional severity sum, and was not much higher for the other self-report scores.

Similar results were obtained in the analogous analysis for age. Again, oddly enough, the correlation with cognitive-emotional severity sum was .00. There was a tendency for older subjects to report a greater number of mixed symptoms (r=.25), a finding not repeated for mixed severity scores. Thus, neither sex nor age was related to expectation, guessing, certainty, severity score or any type of heart rate, signature size, experimenter suspicion, or overall number of symptoms.

The Social Acquiescence scale, the Health Locus of Control, and the MMPI were given as personality tests. The Social Acquiescence scale scores correlated significantly with the F scale (validity) of the MMPI (r=.43, p=.017), perhaps indicating a general desire to please or "look good".

Dahlstrom, et al. (1975) minimize the role of acquiescence in the MMPI, and except for the F scale, these results are consistent with that belief. It was also correlated with the manic scale (r=.55, p=.002), perhaps meaning that if one has manic tendencies, one may be generally more agreeable. The Health Locus of Control scale showed a relationship to hypochondriasis (r=.49, p=.007), indicating that in this sample, those high in hypochondriasis believed they had less control over their health.

The MMPI scales for this sample were highly intercorrelated, as is often found to be the case in other studies (Dahlstrom, et al., 1975; Swenson, et al., 1973). Comparison groups of normals, psychiatric outpatients, and medical outpatients are available (Dahlstrom, et al., 1975), and the present sample clearly was most closely related to the psychiatric outpatient samples. Since it is already known that the scales are intercorrelated, Table 5 provides the correlations that were found in this sample that are higher than any of 10 sample correlations found in the literature. Thus, the L (Lie) and F (validity) scales were correlated -.55 in this sample, while the highest reported correlation was -.10. No correlation was available for the psychiatric sample.

TABLE 5

MMPI INTERCORRELATIONS

	L	F	K	Hs	D	Hy	Pd	Mf	Pa	Pt	Sc	Ma	Si
L		-.55[a] (.10)*	-.65[a] (-.52)						-.41[b] (-.13)*				
F									.68[a] (.57)				
K									-.44[b] (-.29)				
Hs						.83[a] (.75)							
D													
Hy								-.43[a] (--)					
Pd													
Mf													
Pa												.47[b] (.33)	
Pt													
Sc													
Ma													
Si													

N = 26 a = .01 $\leq$ p < .05 b = .001 $\leq$ p < .01

* No psychiatric sample correlation available.

Experimental Dependent Measures

Many of the repeated dependent measures showed a very skewed frequency distribution. Therefore, non-parametric statistics were used in most cases.

Initial breakdowns of means for experimental conditions (screening, base rate, allergen and placebo) showed self-report of symptom severity to be the most sensitive measure of the many used in this study. Accordingly, tests for possible order effects were conducted on this dependent variable. If the severity symptoms were found to vary as a function of the order of trials, this confounding could cloud experimental results. A Friedman two way analysis of variance on severity score for subjects over trials was performed. Severity score was found to significantly differ over trials ($p < .00005$). However, the design deliberately confounded the control groups (base rate and screening) with trial number, since, for example, the first two trials and the last trial were always screening trials. For this reason, the Friedman analysis was repeated on screening and base rate trials only, to discover if, within the control groups, any order effect existed. Results showed no significant difference among these trials ($p > .05$). Therefore, on this sensitive dependent measure, no difference exists among the base rate trials or among the screening trials. Also, no difference exists between the screening trials and

the base rate trials. Therefore, this sample was generally not biologically placebo-reactive. It remained to check whether the allergen/placebo trials differed among themselves (any given trial, by random selection, would contain about 1/3 placebos and 2/3 allergens over all subjects), resulting in an order effect on these trials. A reciprocal transformation of the severity scores (Kirk, 1968) was performed and a one-way repeated measures analysis of variance showed no significant differences among the means ($F=.94$, $df=17,493$; $p > .05$). Therefore, no order effect existed on the experimental trials.

Double-Blind Control Variables

Description. In a double-blind study, it is essential that neither the experimenter or the subject be aware of the identity of the experimental material when it is administered. In order to insure that this was the case, several checks were included in the experiment. Subjects were asked to rate expectations to react before they received the sublingual material. They were also asked to guess the identity of the sublingual material on all trials but the base rate trials, and to rate their certainty of the guess on a 7-point scale from not at all certain to certain.

The experimenter noted any hints given by the subject or any accidental exposure to the experimental material's color. For example, if a subject, contrary to the explicit

instructions, made a comment indicating the substance had a taste, that trial plus all subsequent trials of that substance would be scored as experimenter-suspicious. There were a total of 21 such trials of the 720 given, five of which the hint was actually misleading, since the experimenter guessed incorrectly. This occurred for both placebos and allergens. If by accident the experimenter noted the color of the experimental solution (assuming it was not clear, since in this case it could be either a placebo or an allergen), and thus knew the identity of the substance as an allergen, it was scored as experimenter aware, since there was no possibility of error. There were only three such trials. So all trials could be divided into no suspicion, suspicious-incorrect, suspicious-correct, and experimenter aware. During the course of the experiment, the experimenter noted any such clues provided and scored each trial accordingly. All trials in which any such hints were recorded were placed into either the suspicious-correct, suspicious-incorrect or experimenter-aware category.

Expectations for a reaction were assessed on each trial before the subject received the experimental substance. Expectations were recorded on a seven point scale from "certain I won't react" to "certain I will react." This variable is not merely a control variable, since expectation is hypothesized to influence placebo responsivity, but it should at least be equal for placebo and allergen trials

which are first doses. After the first dose, expectation would probably vary partially as a function of the previous trial's reaction.

Double-blind controls—Results. Guess was scored by the experimenter by strict conservative criteria. If the subject on a given placebo trial guessed water, salt water or saline solution, the guess was scored as correct. Foods, chemicals, other substances and "don't know" were scored as incorrect on placebo trials.

Allergen trials could also be correct, but this is only of secondary interest. The subject was told to expect allergens; if the subject guessed which allergen s/he was receiving it should only influence the self-report or other measures if s/he has a fairly strong belief about how this substance agrees with him/her. In any case, if the subject guessed correctly, it was so scored. When the subject guessed a broad category such as vegetable or fruit, it was not scored as correct since it was exceedingly broad, and the person was unlikely to expect to react to all vegetables. In any case, the majority of guesses on allergen trials were either "don't know" or were incorrect with certainty at "not at all certain."

The mean guess rating (1=correct, 2=incorrect) for allergen trials was 1.97. For placebo trials it was 1.5 and for the screening trials it was 1.24. Overall, 26% of

the guesses were scored correct and 74% incorrect, with highest correct rates in the screen condition, followed by the placebo and the allergen conditions.

Certainty was scored as marked, except that a guess of "don't know" followed by a certainty of 7 (certain) was scored as an incorrect guess, and not at all certain. Certainty ratings were generally low, reflecting a general lack of confidence in one's guesses. The mean certainty rating was only 2.1, with 59% of the trials at "not at all certain." The mean overall certainty ratings for the allergen and placebo trials were virtually identical: 1.81 and 1.98, respectively, while the mean for the screening trials was 3.58.

In order to minimize any concern about removing all placebo aware subjects, most analyses were performed only on the allergen-unaware and placebo-unaware groups, a conservative definition of awareness since it eliminates all trials with the least indication of awareness of the placebo. (Those few trials involving suspicion or knowledge on the experimenter's part were also removed for most analyses.) As a check on this procedure, the mean certainty ratings can be compared for the placebo-unaware and allergen-unaware groups. Since both groups should be blind, they should be equally certain of their guesses. A sign test showed this was the case ($p > .05$). The placebo-aware group could be more certain of their guess than the placebo-unaware group

if they are not all just guessing, and again a sign test indicated that the placebo-aware group was significantly more certain than the placebo-unaware group ($p=.015$, one-tailed).

Water was guessed on allergen trials as well as placebo trials. There were 84 placebo trials on which subjects guessed water with a mean certainty of 2.4. There were also 22 allergy trials on which subjects guessed water with a mean certainty of 1.7.

Experimenter suspicion. With two exceptions, experimenter suspicion was found to occur only on allergen trials, perhaps as one might expect. There were 519 of 540 trials (excluding base rate and screening trials) on which no suspicion occurred. There were five trials on which a placebo was suspected but the substance was an allergen or vice versa, and 13 cases in which an allergen was expected and obtained. There were three trials in which the experimenter became aware of the identity of the solution due to accidental exposure to the color of the solution.

A mean breakdown of experimenter suspicion on severity of symptoms is shown in Table 6. The three lowest means are of most interest. When no experimenter suspicion was present, the mean severity of symptom score was 3.4. When suspicious but not certain, the mean jumped to 11.8. When aware on one occasion of an allergen for all three doses, no reactions

TABLE 6

SEVERITY SCORE BY EXPERIMENTER SUSPICION

Experimenter Suspicion	Mean	S.D.	N
Base rate and screening	2.9*	5.6	180
Suspicious, incorrect	1.8	3.5	5
No suspicion	3.4	5.6	519
Suspicious, correct	11.8	17.4	13
Experimenter aware	0	0	3

*The higher the score, the more severe the symptom.

were reported. The large mean difference of no suspicion and suspicious-correct was compared post hoc by a two-tailed t-test and found not to be significant ($p > .10$). The large mean was due almost entirely to one subject, who was probably the heaviest reactor of any. He reacted very severely on the preceding allergen trial and did the same on this series of three trials. The removal of this subject's trials resulted in a drop of the suspicious-correct mean to 3.85. Therefore, experimenter suspicion had no effect on one of the most sensitive dependent measures.

Expectation. The mean expectation to react on a given trial over all trials was 3.4, with bimodal peaks at 1 and 4. On the 7-point scale used, 1 was certain not to react and 7 was certain to react. Experimental condition means are presented in Table 7. The two control group means are lower than the

TABLE 7

EXPECTATION BY CONDITION

Condition	Mean	S.D.
Allergen	3.91*	1.60
Placebo	3.64	1.56
Base Rate	1.87	1.38
Screening	2.24	1.55

*The higher the score, the more one expects to react. A 7-point scale was used.

experimental group means. The placebo and allergen group means are equal, which seems to indicate true placebo awareness was not too common. In concurrence with this, it could be hypothesized that expectation levels for the first dose of all substances should be the same for allergens and placebos. Dose 1 expectation means were found to be identical (allergen=4.0, placebo=4.1). By the third dose, the two groups still did not differ significantly. Expectation was also examined over trials while removing experimenter-suspicious or aware trials and subject-aware trials. A sign test over trials revealed that no difference in expectation existed over trials for allergen-unaware and placebo-unaware mean expectation ($p > .05$).

Correlational analysis of double-blind control variables. Table 8 shows the intercorrelations of the four variables

Self-Report

The primary purpose of obtaining self-report measures was to assess psychological changes during testing. Since mixed and physical symptoms were also collected, these were analyzed simultaneously, but the major hypotheses of this experiment concerned psychological changes.

Cognitive-emotional symptoms—severity. Symptoms reported by the subjects were classified by judges into cognitive-emotional, mixed, and somatic categories. Cognitive-emotional symptoms included reactions such as "feeling I can't think fast," an aimless, listless feeling, getting tense, irritable, short-term memory difficulty, mind-body split, and confusion. Mixed symptoms reported included various aches and pains and tiredness unspecified as to physical or mental. Somatic symptoms actually reported included hands cold, nasal congestion, shortness of breath, burning in nostril, feeling warmer, visual blurring, and joint stiffening. Severity scores for cognitive-emotional symptoms were summed over each trial. A frequency check showed a markedly skewed distribution, with only 108 of the 720 trials being non-zero. Again, non-parametric statistics were generally used for analysis of this variable, which can be labeled cognitive-emotional symptom sum.

An initial sign test was undertaken on all subjects' mean cognitive-emotional severity sum score over the 18

allergen/placebo trials. A significant difference was found between the allergen and placebo means, such that the mean sums were consistently higher on allergen trials than on placebo trials (N=19, x=2, p=.001).

To rule out a possible "bandwagon effect," in which one reacts more to later doses of a given substance because one knows one reacted to the first dose, this test was repeated on first dose trials only. There was no effect on the above finding. All six allergen means were higher than the placebo means (N=6, x=0, p=.016). The lower probability level is due to a ceiling because of the smaller number of trials.

Because of the possibility of subject or experimenter awareness modifying the dependent score, very conservative tests were carried out on the cognitive-emotional score. All trials on which the experimenter was suspicious or aware or when the subject guessed the identity of the placebo correctly were removed. This had no effect on the outcome of the sign test over trials reported above. Again, allergen-unaware mean cognitive-emotional scores were higher than the placebo-unaware cognitive-emotional mean scores (N=17, x=2, p=.001). Therefore, the significant difference between allergen and placebo mean scores reported above was not due to a lowering of the placebo mean by the placebo-aware scores. This analysis is a strict double-blind test.

A comparison of the placebo-unaware scores to the

placebo-aware scores found no difference between them, indicating no effect of apparently being aware of the placebo on the reporting of cognitive-emotional symptoms. An analysis of dose 1 trials, now with aware trials removed, showed significantly more psychological symptom severity on double-blind allergen trials than double-blind placebo trials ($N=6$, $x=0$, $p=.016$). Thus, removal of aware trials had no effect on the outcome.

A possible confounding factor in the above analysis of all trials was that nine subjects were placebo-aware on all six placebo administrations, although they were not aware on the allergen trials. Could these subjects differ systematically from the other subjects who were not always placebo-aware and thus cause a distortion of the results? The significant difference between allergen and placebo trials could be due entirely to inflated allergen scores of this group. If their allergen scores were consistently higher than those of the remaining subjects, they could artificially inflate the allergen scores as a whole. To test this, placebo-missing subjects were compared to the rest of the subjects on allergen trial mean scores. A sign test (two-tailed) showed the reverse effect occurred; the allergen trial scores of those always placebo-aware were significantly lower than the other group ($N=18$, $x=4$, $p=.03$). If anything, results are strengthened by omitting this group entirely. The sign test over trials was repeated with these placebo-

aware subjects removed, and the results remained the same (N=18, x=2, p=.001).

In order to compare all four conditions, and to assure the strength of the findings, the data were recast into means for conditions over subjects. The nine subjects who were placebo-aware on all six placebo tests were excluded. The mean cognitive-emotional scores for all unaware trials were computed and examined over subjects by a Friedman two-way analysis of variance. The mean comparison for allergen, placebo, and base rate conditions showed a significant difference among the means (x^2=12.4, df=2, p=.002). A Wilcoxon comparison of allergen and placebo scores showed significantly higher mean severity scores in the allergen group under double-blind conditions (z=2.92, p <.002). A sign test comparison of the placebo and the base rate conditions showed no difference (p >.05), and the same was true of the base rate and screening mean cognitive-emotional symptom sums (p >.05). Thus, in this analysis, the allergen condition differed from the other conditions, while there was no difference between the placebo and base rate conditions, and no difference between the base rate and screening conditions.

Cognitive-emotional symptoms—number of symptoms. A measure related to severity scores was number of symptoms. While severity is more sensitive theoretically, it did require adjustment of scores to correct for previous levels of the

symptom. Number of symptoms is more crude, but is a simple counting task. Number of cognitive-emotional symptoms was analyzed separately from severity of the symptoms. Comparing allergen to placebo mean number of cognitive-emotional symptoms over trials with allergen and placebo-aware trials removed, significantly more symptoms were found to be reported on allergen trials (N=18, x=4, p=.015). Placebo awareness-unawareness was found to have no effect on the number of cognitive-emotional symptoms reported.

The nine subjects who were always placebo-aware were found to not differ significantly on allergen trials from the other 21 subjects (p=.10), although a trend existed for the nine subjects to report fewer allergen symptoms. However, their removal and the repetition of the above sign test over trials resulted in a strengthening of the results (N=17, x=3, p=.006).

A Friedman two-way analysis of variance was conducted on the mean number of cognitive-emotional symptoms reported by the 21 subjects over the four conditions. Significant differences were found (x^2=22.8, df=3, p <.00005), meaning that the four conditions were not equal. Dropping the lowest condition, the screening group, a significant difference remained (x^2=13.7, df=2, p=.001). Sign tests were used to compare conditions. Under allergen conditions, subjects reported significantly more symptoms than when exposed to placebos (N=20, x=4, p=.006), while the placebo

scores did not differ from the base rate scores ($p > .05$).

Overall symptoms. Of secondary interest is the overall self-report of symptoms, ignoring type distinctions. Physicians, of course, are concerned about all symptoms, not just the psychological. For all subjects and trials, severity of reported symptoms of all types was greater in allergen trials than in placebo trials ($N=18$, $x=3$, $p=.004$). Omitting all but the experimenter unaware and subject unaware trials had little effect on the overall findings ($N=18$, $x=2$, $p=.001$). The placebo-aware and placebo-unaware trials did not differ.

Examining the group always placebo-aware versus the rest showed no difference on allergen trials, again indicating no biasing effect of their inclusion in earlier tests. Their exclusion from a sign test over trials did not alter the significance of the difference between the allergen and placebo trials ($N=18$, $x=4$, $p=.015$).

The mean symptom severity score over conditions for the 21 remaining subjects on unaware trials was significantly different over the four conditions ($x^2=26.5$, $df=3$, $p < .00005$) and for the allergen, placebo and base rate conditions, a difference persisted ($x^2=15.5$, $df=2$, $p=.0004$). Comparing the allergen and placebo means demonstrated a significant difference, such that more symptoms were found on the allergen trials ($N=21$, $x=6$, $p=.039$). The placebo means were significantly higher overall than the base rate condition

means (N=20, x=2, p <.001), while the base rate condition did not differ from the screen condition. These results generally paralleled those of the cognitive-emotional symptoms, although the placebo effect was absent in the cognitive-emotional analysis.

Overall symptoms—number of symptoms. Overall number of symptoms was analyzed in much the same fashion as above. A sign test of unaware trials showed a significant difference between allergen and placebo trials (N=18, x=2, p=.001), such that more symptoms were reported in the allergen condition. No difference was found on allergen trials for those nine subjects consistently placebo aware and the others, and exclusion of this group did not alter the above effect (N=18, x=2, p=.001).

Allergen and placebo mean scores were compared in a sign test for the 21 subjects across conditions for unaware trials. No significant difference was found, although a trend remained (N=21, x=7, p=.095). The placebo symptoms were more frequent than the base rate symptoms (N=18, x=4, p=.015).

Mixed and physical symptoms. Tables 9 and 10 show the results of the analyses of mixed and physical symptoms, along with the results presented above for comparison. Table 9 is for severity sums, Suml being the sum for symptom group 1 severities (cognitive-emotional), such as difficulty in thinking

TABLE 9

SEVERITY SUM (DOUBLE-BLIND TRIALS ONLY)

	Overall	Sum1	(Sum2)	Sum3	(Sum4)	Sum5
Over Trials	Al > Pl**	Al > Pl**	Al > Pl**	Al > Pl**	Al = Pl	Al > Pl*
	$Pl_{unaware}$ = Pl_{aware}	$Pl_{unaware}$ = Pl_{aware}	--[1]	Pl_{aware} > $Pl_{unaware}$*	$Pl_{unaware}$ = Pl_{aware}	$Pl_{unaware}$ = Pl_{aware}
Over Subjects	Al > Pl*	Al > Pl**	--[1]	Al > Pl*	--[1]	Al = Pl
	Pl > BR**	Pl = BR	--[1]	Pl > BR*	--[1]	Pl > BR*
	BR = Scr	BR = Scr	--[1]	BR = Scr	--[1]	BR = Scr

1. N too small, symptom too infrequent
* .01 ≤ p < .05
** .001 ≤ p < .01

Legend:
Al = Allergen
Pl = Placebo
BR = Base Rate
Scr = Screening
$Pl_{unaware}$ = Trials on which the subject received a placebo and was scored as unaware of the placebo.
Pl_{aware} = Trials on which the subject received a placebo and was scored as aware of the placebo.

TABLE 10

NUMBER OF SYMPTOMS (DOUBLE-BLIND TRIALS ONLY)

	Overall	Num1	(Num2)	Num3	(Num4)	Num5
Over Trials	Al > Pl**	Al > Pl*	Al > Pl**	Al > Pl**	Al = Pl	Al > Pl*
	$Pl_{unaware}$ = Pl_{aware}	$Pl_{unaware}$ = Pl_{aware}	--[1]	Pl_{aware} > $Pl_{unaware}$**	$Pl_{unaware}$ > Pl_{aware}*	$Pl_{unaware}$ = Pl_{aware}
Over Subjects	Al = Pl	Al > Pl**	--[1]	Al > Pl*	--[1]	Al = Pl
	Pl > BR*	Pl = BR	--[1]	Pl > BR*	--[1]	Pl > BR*
	BR = Scr	--[1]	--[1]	BR = Scr	--[1]	BR = Scr

1. N too small, symptom too infrequent.
* $.01 \leq p < .05$
** $.001 \leq p < .01$

Legend:
Al = Allergen
Pl = Placebo
BR = Base Rate
Scr = Screening
$Pl_{unaware}$ = Trials on which the subject received a placebo and was scored as unaware of the placebo.
Pl_{aware} = Trials on which the subject received a placebo and was scored as aware of the placebo.

or irritability. Sum3 is the same for mixed, such as aches and pains, and Sum5 is for somatic symptoms such as feeling flushed or perceiving heart rate changes. Sum2 and Sum4 are for symptoms that the judge did not agree on. They are much less frequent than the others, and are therefore probably less reliable. Sum2 symptoms included "things echo-ey and far away," feel slower, and pain across top of head when writing or thinking. Sum4 symptoms reported included pressure on ears, dizziness, and feeling shaky. The first row grouping concerns the comparisons of allergen to placebo trial means, and below that is found the comparison of placebo-aware and placebo-unaware scores. The second row grouping summarizes the findings for the condition means over the 21 subjects who were not always placebo aware. Only unaware trials are included in the analyses. Below this is found the comparison of placebo and base rate conditions over subjects, as well as base rate to screening.

Table 10 is a parallel table listing the results of the same analyses on number rather than severity of symptoms. Thus Type1 refers to the number of symptoms for the cognitive-emotional category. In general, the results are similar for all four sets of analyses. This is especially true of the cognitive-emotional symptoms, which are uniformly significant, while placebo cognitive-emotional symptoms are no greater than during the base rate condition. Mixed symptoms (3) are also always greater in allergen than placebo conditions.

An unexpected finding was that significantly more mixed placebo symptoms occurred in "aware" trials than unaware trials. This probably indicates that the awareness criterion is too conservative, but the data were analyzed above with all trials included, with similar significant results. This finding could also support the interpretation that delayed reactions or carry-over effects were showing up as mixed symptoms.

For both dependent measures of physical symptoms, analysis over trials indicated significantly more symptoms on allergen than placebo trials, while the placebo unaware and placebo-aware symptoms did not differ. Analyzed over subjects, no difference is found between allergen and placebo trials, while physical placebo symptoms are found more frequently than base rate physical symptoms.

The overall severity and symptom frequency analysis found significant differences between allergen and placebo scores on three of the four analyses. The analysis over subjects for number of symptoms overall failed to achieve significance ($p=.096$), but this effect would be due to the combination of two factors: (1) the physical symptom group also failed to achieve significance by this analysis, while the strongest results were found in the cognitive-emotional group. But there were 92 non-zero cognitive-emotional trial scores (there were 720 trials overall), while the mixed and physical symptoms had almost 150 non-zero trials each. In

the combined analysis, the contribution of the cognitive-emotional symptoms may have been masked by the greater weight carried by the other two groups. (2) the analysis over subjects, in exploratory research, may cover up the reactions of a minority of large responders with those who are not responding allergically. Analyzing over trials allows a few large respondents to carry the group mean, a result which certainly is valid in trying to establish the existence of a phenomenon. It may be that physical symptoms in particular, in this group selected for psychological symptoms, were more prone to placebo influence, perhaps because these symptoms were not as salient to the subjects as their psychological complaints. On the other hand, the cognitive-emotional symptoms showed no placebo responsivity whatsoever.

A problem with the above analysis is that multivariate non-parametric techniques are not readily available. The large number of statistical tests in Table 9 and 10 could result in some chance findings. It should be recalled that the primary purpose of this research is the examination of psychological effects of allergen testing, so other analyses are secondary in determining significance.

One way to increase confidence in the results is to find highly intercorrelated dependent measures, combine them, and then test for significance. It was found that each of the severity variables was highly intercorrelated with its

number of symptoms counterpart, with Kendall correlations ranging from .91 to .99 (Table 11). Therefore, Typel and Suml were transformed to z-scores, averaged together, and allergen and placebo groups were compared by a Wilcoxon matched-pairs signed ranks test over the 21 subjects eligible. The results remained significant under the double-blind conditions ($z=-2.93$, $p < .002$). The same procedure was followed for the mixed category with significant results ($z=-2.29$, $p=.011$). The allergen and placebo trials did not differ on the physical symptoms ($p > .05$).

Severe reactions. Subjects would occasionally require medical attention to relieve severe reaction apparently engendered by testing. These were relatively infrequent, and individual variability was present in frequency of requesting attention. Fortunately, no patient needed relief so badly that s/he was unable to complete all three doses. Uncomfortable reactions are typically treated by administering a neutralizing dose of the test substance or by giving oxygen for up to five minutes. In general, neutralizers are given in more serious reactions. As described above, they were administered by a medical assistant under conditions of both the experimenter and subject being blind as to its identity. If a placebo administration culminated in a request for a neutralizer by the subject, the assistant was to provide a placebo neutralizer. On five occasions during allergen/placebo testing the subject

TABLE 11

KENDALL INTERCORRELATIONS—SELF-REPORT[1]

	Sum1	Sum2	Sum3	Sum4	Sum5	Overall Number	Num1	Num2	Num3	Num4	Num5
Overall Severity	.48	.24	.60	.36	.63	.91	.47	.24	.58	.36	.61
Sum1		.18	.16	.17	.16	.46	.97	.18	.15	.17	.15
Sum2			.05*	.07	.12	.23	.17	.99	.05	.07	.12
Sum3				.18	.32	.60	.16	.05	.95	.18	.32
Sum4					.27	.38	.18	.07	.19	.98	.26
Sum5						.65	.16	.12	.33	.27	.95
Overall Number							.47	.23	.62	.38	.67
Num1								.16	.15	.18	.15
Num2								.05	.05*	.07	.12
Num3										.19	.33
Num4											.27
Num5											

1. All correlations significant at $.001 \leq p < .01$ unless otherwise indicated.
* $.01 \leq p < .05$

requested a neutralizer. Breaking the codes at the end of each day revealed that all five were on allergen trials. A sixth neutralizer was given to subject #9, a heavy reactor, who reacted very strongly on several consecutive substances. She continued to react severely during the final base rate and screening trials, and so was provided a neutralizer for the last allergen/placebo trial given to her, on the assumption that the symptoms were due to a continuation of symptoms from that test. It was beef, an allergen.

On 18 occasions a neutralizer and/or oxygen was given to relieve a reaction. On only two of these occasions, both oxygen relief, the request followed a placebo. Frequency of neutralizer and oxygen requests were compared on allergen and placebo trials by means of a proportional sign test. Results showed that requests for medical attention occurred significantly more frequently on allergen than on placebo trials ($N=9$, $x=1$, $p=.02$).

The two placebo trials on which oxygen was requested are suspicious, since on both occasions, the immediately previous allergen (the previous substance) had engendered a reaction so severe as to require a neutralizer or oxygen. Severe reactions are logically most likely to spill over to the next test. Also, on both placebo occasions, the person had guessed water as the substance on the last dose, which preceded the request for aid. If we remove all suspect occasions of medical aid by omitting all trials when

relief was requested for one substance chronologically immediately following another such occasion, 14 occasions remain, all of which are allergen trials. A proportional sign test over subjects was significant (N=9, x=0, p=.002).

Heart Rate

Heart rate during pilot testing and for the first few experimental subjects was recorded once before and once after the dose. Finding too much background variability, three readings at 30 second intervals were taken during the remainder of the experiment. Mean scores were used for analysis. An initial breakdown of the mean change on heart rate showed that the means were swamped by standard deviations roughly 30 times their magnitude. Since its distribution was not normal, further non-parametric tests were conducted.

On double-blind trials, pre-dose heart rate was equal on allergen and placebo trials by a sign test ($p > .05$), and the same was true of post-dose heart rates ($p > .05$). The differences between post-dose and pre-dose heart rates were compared and found to be the same, but a serendipitiously uncovered result was that the standard deviation on allergen trials was significantly larger than on placebo trials (N=18, x=3, p=.004). This finding is completely *post hoc*, and so must be viewed with caution. As a check, the standard deviation of the placebo-aware trials and

placebo-unaware trials were compared and found to be identical. Allergen and placebo standard deviations were compared on pre-dose heart rate measures and also on post-dose heart rate measures. In both cases they did not differ.

Taking the absolute value of heart rate change produced no significant differences between the means ($p=.119$), but the same findings for the standard deviation of allergen and placebo trials was obtained ($N=18$, $x=3$, $p=.004$). The latter finding is perhaps not unexpected since it involves a simple transformation of the data. If this finding is meaningful, it indicates a wider spread of change on the allergen trials than the placebo trials, although the means do not differ.

There were a number of problems in recording heart rate. Continuous monitoring with peak comparisons may be much more revealing than the present crude technique. The rigid heart rate recording schedule adhered to for this study and the possibility for error in reading an analog dial combined to allow observed sudden jumps in heart rate and brief erratic beating to go unrecorded.

Signature

Signature was found to be related to self-esteem (Zweigenhaft & Marlowe, 1973), and so was used in this case to check for mood changes. Area covered by the signature was estimated by multiplying the height of the longest

letter with the width of the signature. Since the distribution was skewed, means and standard deviations were examined by non-parametric methods.

Initial analysis of double-blind trial means revealed significant differences on means such that allergen trials had larger signatures than placebo trials ($N=18$, $x=0$, $p < .001$), and on standard deviations ($N=18$, $x=0$, $p=.001$) such that more variability was found on allergen trials. However, closer analysis showed these results to be artifactual. The allergen responses of those who were aware on all placebo trials and those who were not were significantly different on means ($N=18$, $x=0$, $p < .001$) and standard deviations ($N=18$, $x=0$, $p=.001$). Their removal followed by a repeat of the above analysis caused the significant effect to vanish ($p > .05$) for both variables. A mean comparison over the 21 subjects found all conditions (allergen, placebo, base rate and screening) to be equal. Some dependent measures, as shown in Table 4, were only given on one of the three doses for each of the test substances. These dose-related variables will be discussed below.

Dose 1 Variables

The 270 Bender-Gestalt drawings were scored by an individual trained and experienced in its use. Blind as to condition, the judge scored each drawing on a four point scale. A mean breakdown clearly showed no difference

between allergen and placebo conditions, as did a sign test over trials ($p > .05$). A few drawings showed apparent rotation, a serious distortion, but since how the subject placed the page was not marked, it was not certain whether these were true rotations or simply due to unusual positioning of the paper. A separate scoring for presence or absence of rotation produced no difference between conditions, the means being virtually identical.

The uses of test was scored for flexibility (number of categories) independently by two blind judges. The experimenter counted the raw number of responses (fluency). Both these measures failed to distinguish between conditions.

The mean time estimation of one minute was the same for allergen and placebo conditions. Deviation scores were computed by taking the absolute value of the estimate in seconds minus 60. Inspection of the means showed no difference between allergen and placebo conditions.

Dose 2 Variables

The Mood Affect Adjective Check List was scored according to the standard procedure of the authors. Anxiety, depression and hostility were all found to have no mean difference between conditions. One peculiar phenomenon occurred several times in regard to the mood scale. The subject would make no checks on the mood scale at all and return it saying "Nothing fits how I feel" or "None apply." Checking the

scales showed five instances of this behavior, four allergen trials and once on the final screening trial. Subject #8 repeated this behavior on the last allergen (F) and then on the following screening trial. Thus, this behavior never occurred on a placebo trial. Unfortunately, it was so unusual as to preclude statistical analysis.

The number cancellations task was scored for both the number correctly marked and number of errors. The latter was found to almost always consist of omissions rather than crossing out the wrong number. In both cases, condition means were virtually identical.

Dose 3 Variables

The WAIS Digit Symbol Substitution Test was scored in the standard manner. In scoring, several instances of distorted or even bizarre numbers were found by the experimenter. These were analyzed separately. Means for the conditions were again almost identical in both cases.

The WAIS Block Design Test was scored as the time in seconds to complete the task. If the subject made an error or took longer than three minutes, 180 seconds was assigned as the score. This procedure was necessary since on several occasions subjects could not complete the design and had to give up. No difference was found between the conditions.

The graphic constriction-expansion task was scored

as described above. Again, no relation was found between experimental condition and mean size of the doodle.

Correlational Analysis

Pearson correlational matrices of the variables produced many correlations that were significant because of the large number of trials, rather than because of the large amount of variance accounts for. Because of the number of correlations and the post hoc nature of this analysis, only correlations of .30 or above were examined. Lower correlations, although significant, account for less than 10% of the variance and are therefore minor influences on the data.

Table 12 provides the significant correlations obtained broken down by experimental condition. Obvious or trivial correlations are omitted, such as intercorrelations between theoretically related measures. For example, uses of fluency and flexibility were closely related, but neither was significant in the data analysis. Likewise, the heart rate measures were intercorrelated, but in general the dependent measures were not related to each other.

Expectation was related to both overall number of symptoms and overall severity of symptoms, especially in the placebo condition. For overall severity, the allergen correlation does not appear to differ from the base rate condition. It had been hypothesized that expectation would be related to symptoms for both allergen and placebo trials,

TABLE 12

PEARSON CORRELATIONS (SIGNIFICANT) BY EXPERIMENTAL CONDITION

	Allergen	Placebo	Base Rate	Screening
Expectations with overall number of symptoms	.36**	.37**	.26**	.20*
Expectation with overall severity of symptoms	.25**	.34**	.23*	.13
Expectation with Num4	.20**	.39**	.18*	.25**
Expectation with Sum3	.24**	.30**	.15	.18*
Expectation with Sum4	.18**	.38**	.18*	.21*
Guess with certainty	-.10*	-.30**	--	-.26**
Signature with guess	-.07	-.37**	--	-.10
Pre-dose heart rate with post-dose heart rate	.88**	.93**	.94**	.92**
Pre-dose heart rate with signature	-.26**	-.29**	-.31**	-.22*
Post-dose heart rate with signature	-.19**	-.26**	-.31**	-.20*

* $.05 \leq p < .01$

** $.01 \leq p < .001$

but that the relationship would be stronger for the placebo trials. The number of symptoms 4 group was related to expectations, especially for placebo trials, as was the case for severity sum for mixed symptoms, and for severity of category 4.

The guess with certainty relationship indicates that for the placebo trials, correct guesses were associated with higher certainty. Few allergen trials were guessed correctly.

The signature with guess correlation for placebo trials confirms what was discovered above, that those who guessed correctly on placebo trials tended to have larger handwriting, a confound that was corrected. Oddly enough, the pre- and post-dose heart rate correlated in the base rate period with signature size such that those with lower heart rates had larger signatures. This is consistent with the link to mood traits reported (Zweigenhart & Marlowe, 1973), in that perhaps those with higher self-esteem (larger handwriting) may be more relaxed.

Finally, pre-dose heart rate and post-dose heart rate were very highly correlated. However, the pattern of correlations is perhaps indicative of a trend for the least relationship between the two to be found in the allergen condition. It is possible that better recording techniques would reveal a more convincing relationship. It would certainly be premature to abandon heart rate as an allergic indicator at this time.

Some of the negative findings of interest are shown in Table 13. Expectation was not related to severity of symptoms for any category (1, 3 or 5) for allergen trials, nor to the number of symptoms in these categories. Category 3 (mixed) symptoms were related to the placebo condition for both number of symptoms and severity of symptoms. Expectation level was not related to dose number, as a chronological variable. In terms of allergen trials, dose levels are not necessarily on even an ordinal scale, and so little relationship would be expected.

TABLE 13

PEARSON CORRELATIONS (NON-SIGNIFICANT) BY EXPERIMENTAL CONDITION

	Allergen	Placebo	Base Rate	Screening
Expectation with Sum1	.19**	.03	.08	.18*
Expectation with Sum3	.24**	.30**	.15	.19*
Expectation with Sum5	.12*	.16*	.22*	-.07
Expectation with Num1	.23**	.08	.20*	.17
Expectation with Num3	.28**	.31**	.14	.09
Expectation with Num5	.18**	.15*	.22*	.07
Expectation with dose number	.00	-.18**	--	--

* $.05 \leq p < .01$

** $.01 \leq p < .001$

CHAPTER IV

DISCUSSION

Psychological Effects of Allergens—Self-Report

The major hypothesis of this experiment was that greater psychological effects would be found on allergen trials than on placebo trials. Self-report data strongly supported this hypothesis, showing that for all methods of analysis used on these symptoms, cognitive-emotional symptoms were significantly greater than placebo symptoms. It is of great importance to bear in mind that these results were obtained under strict double-blind conditions, with any indication whatsoever of awareness being grounds for removal of that trial or subject from analysis. In fact, it made little difference whether "aware" trials or subjects were excluded from the analysis since similar results were obtained. Also, no placebo effect was found for cognitive-emotional symptoms, since placebo symptoms of this type were no greater than base rate symptoms of this type.

These symptoms were unambiguously cognitive-emotional, since both judges had to categorize a symptom as cognitive-emotional in order for it to be included in this group. When number of symptoms was collapsed with severity

of these symptoms, results remained highly significant ($p < .002$). Because of the strength and reliability of these findings, we can infer that when cognitive-emotional symptoms are reported under similar testing circumstances, they are indeed due to allergen exposures or else they are simply "background noise" that would have occurred whether the person was tested or not.

More importantly, this research confirms that it is possible for "psychological" or "psychiatric" symptoms to be induced entirely by a non-personal agent, in this case, an allergen. No one is surprised if such symptoms are induced by a drug, in which a physical agent is responsible for psychological changes. The phenomenon researched here bears many similarities to drug effects, except that the most common causal agent in this case is not a drug not normally found in the human body, but foods. Foods are normally considered incapable of effecting meaningful changes in consciousness, but some subjects certainly experienced drug-like effects to minute sublingual doses of foods.

The cognitive-emotional symptoms reported on allergen trials included such diverse symptoms as feeling "merry," "out of it," "brain in fog," "pissed off" at no object in particular, detached from the body, nervousness, severe depression, and severe mental blankness. One subject began giggling and laughing to herself, and later reported

that she had started to think of absurd things and felt giddy. A change in her demeanor was apparent, since she had not laughed much earlier. In another case, a subject received a placebo for the first substance and reported reactions similar to base rate reactions. On the next substance, he reported symptoms of all types, including severe mental slowness and a feeling of being drugged like on a sleeping pill. (This last symptom was scored as in between cognitive-emotional and mixed.) After this reaction on the third dose, the subject wanted to quit and go home. He was given oxygen, but received little relief. He then took a walk, which also failed to clear the symptoms. A relieving dose (neutralizer) was then given by a medical assistant, which resulted in complete relief of symptoms, according to the subject. He reported that after relief, things even looked different, since they had looked closed in and dark. These symptoms were reported after the dose and so were not scored. The allergen was cane sugar.

On another allergen on another day, the same subject reported very severe loss of motivation and very severe inability to concentrate on the Block Design Task. He also felt drugged, like being controlled by something outside of himself or restrained. Intellectually, he knew this was not the case, but the feeling reminded him of when he had been in a mental hospital previously. Other types of symptoms were also reported by the subject for this allergen, which

was milk. The identity of specific offenders for particular individuals is not the major focus of this research, since what is an allergen for one individual may have no effect on another. What is important is to provide a feeling for the kind of cognitive-emotional symptoms reported by subjects.

Other Measures

Other measures of psychological performance or mood failed to indicate any change due to allergen exposure. The single physiological indicator, heart rate, suffered from the flaws mentioned above—a rigid recording schedule, too few data points on each trial and the subsequent failure to record observed variability in heart rate on many occasions. For example, any heart rate increase occurring between the fourth and tenth minute was inevitably lost, since the single experimenter could not record heart rate and carry out the other experimental activities. In spite of these difficulties, the heart rate changes were in the right direction, although not significant ($p=.119$), and further more careful investigation of this variable is justified. Also, a significant *post hoc* finding ($p=.004$) of greater variability of change in the allergen group indicates that this variable may provide useful data under more careful conditions. It could very well be that heart rate changes occur only in certain individuals and/or only at certain stages

or dose levels of a reaction. This could reconcile the findings here reported with clinical experiences of occasional dramatic changes in heart rate.

Why did self-report provide such strong support for psychological symptoms as a function of allergen exposure while the other performance and mood dependent measures did not? There are a number of possibilities which are important in that, if they may lead to a more efficient and powerful test of future hypotheses in this area. First, even for self-report, reactions of any kind were only reported on 291 trials of the 540 allergen-placebo trials given. For double-blind trials only, no reaction occurred on 60% of the placebo trials and 41% of the allergen trials. But the same analysis on cognitive-emotional symptoms finds no such symptoms on 90% of the placebo trials and 79% of the allergen trials. Many doses of the allergen were therefore in actuality placebo doses. Since an allergen is defined by its provoking reactions, a substance that fails to provoke any reaction in a given individual is not an allergen for that individual. This happened because it was necessary due to financial and time constraints to use suspected rather than known allergens in testing. Often, suspicions were incorrect, resulting in the administration of a placebo as an allergen. Practical constraints ruled out one solution to this problem, which is to pre-test and repeat substances providing reactions. This was not possible due

to the time constraints of the patients, as well as their general and understandable unwillingness to repeat substances that apparently produced severe reactions in them.

Just as in drug research, a true allergic reaction is the summated effect of the placebo, the active substance itself, and the base rate of reactions. Thus, in allergy testing, R = A + P + BR + E, where R is the reaction, A is the allergen effect, P is the placebo effect, BR is the base rate of the symptom, and E is error. For placebo trials, the equation is R = P + BR + E. If a given allergen dose has an A component of 0, the net effect is to lessen the efficiency of the design in detecting genuine allergic reactions, since the allergen equation becomes equivalent to the placebo equation.

Ideally, then, the allergen trials should have a reaction on at least one of the doses. By pre-testing, only known offenders need to be included in the research. One caveat is necessary, though: the pre-testing may sensitize patients to the identity of the allergen if it has a distinctive taste. They may then expect the same reaction they had during pre-testing to this particular substance.

A second factor affecting the negative results for performance measures is the rigid schedule for the administration of these measures. A major distinction between self-report and the other measures is that only self-report is cumulative, that is, the subject collects symptoms from

the entire ten minute period and reports them to the experimenter. A few subjects would even write notes to themselves on their symptoms as they appeared, and many preferred to mention them as they occurred. Quite a different result might have been obtained if the subject were only allowed to report the symptoms they were experiencing during a set one or two minute period within each trial, as was the case for all other dependent measures. Reactions are often fleeting in test situations, and so may be easily missed by "fishing" at the wrong time.

Another related factor is that self-report was all-encompassing of symptoms, while the other measures were generally more narrow. For example, if one were experiencing only difficulty in concentration as an allergic reaction, no change should occur on a mood scale. The probability of having the mood scale administered at the same time as a mood change occurs may be quite low. Self-report would always allow for the reporting of such a symptom, however.

A fourth factor in the negative performance results is the ability to compensate while reacting to prevent deterioration in performance. A subject may be aware of the reaction and compensate by increased effort, thus obscuring the effect of the allergen if the reaction is not virtually incapacitating. Cursory examination of performance on several trials on which subjects reported difficulty in concentrating on the task showed no obvious effect, a result

consistent with the above hypothesis. More stressful or prolonged tasks might have shown a decrement, but were not practical or desirable for this initial experiment.

It is also true that if deliberate feeding in normal doses was done, more dramatic and incapacitating reactions may be incurred in susceptible individuals. However, such reactions are undesirable to the patient, are not blind, and may take much longer to appear and disappear. These tests are clinically performed after fasting.

Somatic and Mixed Symptom Self-Report

Mixed symptoms were found to be greater in allergen trials than placebo trials, indicating that symptoms such as headaches, aches and pains, and fatigue (unspecified as to whether physical or mental) can be induced by allergens. Many of these symptoms are commonly labeled "psychosomatic" and are believed psychological in origin. Psychological causation was not the primary origin of most of these symptoms in this experiment. Yet it would seem quite likely that the subjects in this experiment would risk neurotic labeling if seen for these complaints by a mental health professional, as shown below:

> Interspersed between TV commercials for headache tablets, muscular relaxants, intestinal tonics and the like, we manage to see a few of the other forms of entertainment provided to meet the public demand. It has often been noted that more ingenuity is invested in attracting the American populace to remedies for their non-existent ailments than in filling their impoverished imaginations.

> There are many reasons for the vast and continuous commercial success of these nostrums. Primary among them is the need of millions of Americans to find magical elixirs and balms by which they hope, rather futilely, to counter their lack of energy and a bevy of minor physical discomforts. These perennial states of fatigue and the persistence of medically undiagnosable aches and pains signify another of the neurotic disorders, one that . . . disables, in one form or another, a significant portion of our population. (Millon, p. 412)

It could indeed be unfortunate for an allergic patient to encounter such an attitude towards his/her discomfort.

Somatic symptoms were found to be greater over trials on allergen than placebo trials, but when analyzed over subjects, the difference vanished. These symptoms included itching, nausea, stuffy nose, coughing, sore throat, muscle cramps and feeling flushed. It is odd that such clearly bodily symptoms should be less convincingly due to allergens than cognitive-emotional and mixed symptoms. After all, physicians accept that allergies can cause a gamut of physical reactions, and this study was necessary to examine the more controversial cognitive-emotional symptoms, not the somatic. How can this unexpected finding be explained? The inconsistency of finding significance over trials but not over subjects suggests that a few subjects may be reacting heavily physically to the allergen, while most subjects do not react differentially to the allergen and placebo. It is also possible that physical symptoms are more prone to be delayed reactions than other symptoms. Symptoms are reported to oscillate, according to Randolph's stimulatory-withdrawal

model, and for this sample it could be that the nervous system is more sensitive than other tissues, as others have suggested (Pauling, 1968). Thus, a reaction may appear early in the form of cognitive-emotional symptoms and later in the form of somatic symptoms. Perhaps higher centers of cognition and emotion are affected earlier and more easily than lower centers controlling bodily functions, as is the case in alcohol consumption.

If delayed reactions were common, we would expect greater reactions on the final base rate and screening trials than on the initial ones. This was not the case. This could be due to a confounding of attention levels and threshold to report symptoms with experimental condition. In other words, subjects may suppress reporting of symptoms during base rate periods because they knew it was not an allergy test reaction, but during allergen/placebo trials they may report doubtful symptoms rather than risk omitting a clue to their illness. This hypothesis of delayed reaction for physical symptoms combined with base rate suppression may account for the failure to obtain significance over subjects, but it is speculative. The base rate suppression mechanism, incidentally, is a valid placebo effect, in that when it is not in effect, such as on placebo trials, more symptoms will be reported.

Another possibility is that our sample of patients selected for cognitive-emotional complaints simply tended

to forget to mention physical symptoms when cognitive-emotional symptoms were present. The latter symptoms are of greater interest to the group since they complained mainly of them, and so the physical symptoms may have been less salient.

No matter what the explanation, analysis over trials in which a few large reactors may have carried the group is valid, since this experiment concerns the existence of a phenomenon, not its generalizability. This analysis was significant for somatic symptoms. Therefore, we may assume the allergen-induced somatic symptoms were greater than placebo-induced somatic symptoms.

Severe Reactions

Relief from the effects of reactions was requested significantly more often on allergen trials than placebo trials. The omission of suspicious trials produced no requests on placebo trials, a strong indication that under double-blind conditions severe reactions were engendered by allergens and not by placebos.

Placebo Reactions

A secondary hypothesis of this experiment was that placebo trials would evoke greater reactions than base rate conditions. This was only partially supported. For cognitive-emotional symptoms, no placebo effect was found, which was

surprising in view of the more "psychological" nature of the symptoms. Mixed and somatic symptoms were greater on placebo trials than on base rate trials. Contrary to the belief of some clinical ecologists, such symptoms can apparently be placebo symptoms at times. However, delayed reactions can not be ruled out. As mentioned above, subjects frequently seemed to consider the base rate periods as either puzzling in spite of the instructions or as a rest period. If true, delayed reactions would not be accessable in this study.

Placebo symptoms would not be surprising if they did occur for mixed and somatic symptoms. A certain proportion of asthmatics, for example, are apparently placebo-reactors and a certain proportion are consistently unresponsive to placebo influence. Whether the former group is even allergic is not clear. But the patients in this sample were not generally known to be allergic either, and could certainly contain some placebo reactors. Perhaps those who reported primarily somatic and mixed reactions were more prone to be placebo-reactors.

In many cases, the placebo was equal to the base rate. This was true for cognitive-emotional symptoms, heart rate, signature size, uses of scores, time estimation, Mood Affect Adjective Check List scores, and the cancellation task. The signature size standard deviations were in the wrong direction (more variability during base rate). The same

Bender-Gestalt cards were always presented during the base rate period, so this variable is not useful for comparing base rate to placebo. Likewise, the dose 3 dependent variables were not given during the base rate. So only on mixed and somatic symptom self-report of all the eligible dependent measures was a significant placebo effect found. Thus, it is more logically proper to say, in regard to these performance and mood indicators, that no effect occurred whatsoever than to say the allergen trials were no greater than the placebo trials. Actually, neither differed from base rate, and therefore sheds little light on whether clinical symptoms reported in the literature are due to psychological (placebo) causation or physical (allergen) causation.

Expectation

Expectation was hypothesized to be more closely related to placebo symptoms than allergen symptoms, since the allergen component, if biological and not just a placebo, would be unpredictable to the blind subject, at least on the first dose. Expectations were found to account for little of the variance in reported symptoms, except for mixed symptoms on placebo trials (r=.30). Expectations were not related to dose number for allergens, perhaps meaning that allergen reactions were not predictable, and expectations for the later doses were influenced by earlier doses.

Personality Tests

The clinic sample as a whole was generally pathological in pattern on the MMPI, but was similar to asthmatic samples and to psychiatric outpatients. The questions that must be raised, based upon the results of this experiment, are: To what degree is the pathology of these patients due to allergy? How much, if at all, would alleviation of allergies affect future MMPI scores? For these patients, are these mental symptoms primarily due to allergies or does allergy simply trigger the effects? These questions are out of the scope of the present research. However, if allergy plays a significant role in the pathology, diagnosis and treatment is essential for complete recovery.

The Social Acquiescence scores showed this group to be lower on acquiescence than a group of normals. This finding could be taken at face value, or it could be due to the passage of 20 years since the test was standardized. If taken at face value, it would indicate that these subjects may be less prone to placebo reactions than normals. The sample was also no more or less internal than normals on the Health Locus of Control, although appropriate medical and psychiatric comparisons were not provided.

Conclusions and Implications

The clear demonstration of cognitive-emotional changes occurring following allergen exposure under double-blind conditions suggests that a connection between allergens and our psychological state can no longer be dismissed or overlooked. Replication of these findings and further evidence for an exploration of this effect are needed.

It could be argued that the cognitive-emotional changes that occurred were due to somatic mediation—the body may have provided cues that triggered the cognitive-emotional symptoms. This would seem unlikely to an observer of these reactions, for several reasons. First, the cognitive-emotional symptoms often occurred unaccompanied by any reported somatic or mixed symptoms. Possibly, the person was withholding symptoms or was not aware of these cues, but this possibility is unproven and without any evidence. It seems unlikely that one would have severe feelings of being drugged or controlled by something outside of oneself, as one subject reported, because of a stuffy nose that was reported on the same trial.

Another reason for discounting this possibility is that the somatic symptoms and mixed symptoms had placebo components and were weaker than the cognitive-emotional symptoms. The cognitive-emotional symptoms were more robust and had no placebo effect—the placebo symptoms were the

same as base rate symptoms. The only way to rule out somatic mediation is to prevent any somatic cues from reaching the brain, such as by curarization of the entire body, except the brain. One would be hard-pressed to secure volunteers for such a study. Proof of no somatic mediation may therefore be impossible in practical terms, but the evidence does make this possibility unlikely. It would require a rather unwieldy set of assumptions to explain all cognitive-emotional symptoms as mediated in this study.

In regard to these symptoms, it must be emphasized that they in no way need to be linked to reported bodily complaints. There is no reason to assume somatic cues mediated the sometimes very severe cognitive-emotional symptoms obtained here, since such symptoms often occurred independently of mixed and somatic reported symptoms. The intercorrelations of cognitive-emotional severity sum was negligible with the other categories, since no correlation was as high as .20 (Table 11). The lack of support for somatic mediation strengthens the claim of the clinical ecologists that cerebral allergies can exist independently of physical allergies, although not proven by this research since it was not directly tested. The data indicating a possible alternation of asthma and psychosis (Leigh & Marley, 1967; McGovern & Knight, 1967; Freeman, et al., 1964) would also support this possibility.

The lack of a placebo effect for cognitive-emotional

symptoms is surprising, since such psychological states are often viewed as being particularly prone to psychological manipulation. This finding implies that the physician employing sublingual testing can place greatest confidence in symptoms of this type.

It could be argued that self-report is unreliable and not to be trusted. The results of this experiment clearly show that self-reported symptoms can be meaningful, since when unaware of what they were receiving, subjects still reported more symptoms to the allergen than to the placebo. Also, self-report of internal states carries tremendous ecological validity. Ones does not consult a physician or therapist because one notices a decrement in one's performance on a cancellation task; one usually goes because of not feeling well. Subjects came to the clinic because of symptoms they experienced, not because of objective test scores.

What are the implications of these findings for medicine and psychology? It would seem quite appropriate for both fields to explore more closely the relationship of mind and body in allergy. A cursory examination of the 1977 Indicus Medicus showed no research in medicine in this area, while Psychological Abstracts had only one or two for the same year. Yet these findings are quite consistent with research showing mood changes in asthmatic children (Weiss, 1966). The double-blind results of dietary changes on

hospitalized schizophrenics (Dohan & Grasberger, 1973; Dohan, et al., 1969) is consistent with the results, but has apparently received little attention in either field.

If we accept the present findings, what is the role of allergy in the mentally ill? One study of hospitalized mental patients of all types found 90% of the schizophrenics to react, but no group stood out as failing to react (Newbold, Philpott & Mandell, 1973). As noted above, proper controls were lacking. Even if true as reported, these results would only demonstrate allergy as a trigger of symptoms. Removal of allergic reactions would enable the researcher to examine what portion of symptoms are attributable to allergy.

One patient was discussed above who had symptoms similar to when he was hospitalized for psychiatric symptoms during testing. Another patient related to me how he had been in group therapy for his problems. Failing to help, he turned to medicine where he was diagnosed as hypoglycemic and placed on a diet heavy on protein. He consumed a lot of beef and was improved for a time. He then got worse. He received a beef test first under experimental conditions and reported the return of a headache and an inability to think clearly on the first dose. On the second dose his headache increased, he described his mental processes as feeling like his brain was in a fog, and was sleepy. On the third dose, all three symptoms got worse. He failed to react on any placebo trial and was unaware of the placebo.

Overconsumption of beef in an allergic individual could generate a new allergy.

This patient apparently had a heavy burden of guilt or concern about his psychological problems. When he found the symptoms reported above could be treated as being due to beef, he was visibly relieved.

These controlled results imply that the psychologist must be very cautious in determining etiology and treatment for "psychological" disturbances. Our profession and lay culture too readily blames the victim or parents for psychological disturbances. Yet, here, psychiatric symptoms were literally turned on and off in patients, a feat not equaled by psychological approaches. The glib assumption of psychological causation for psychological symptoms originates perhaps in the Freudian and neo-Freudian approaches to mental illness. Yet, psychoanalysts would be hard-pressed to explain these findings in the light of their theories.

A few words of caution are appropriate to prevent over-generalizing these results. Only adequate allergy treatment will provide information on the portion of symptomatology due to allergy. In terms of mental illness, anywhere from a small fraction to 90% of the patients may benefit from allergic management. No properly controlled study exists to delineate the magnitude of the allergic problem. The present study is internally-valid, and thus establishes the existence of a phenomenon. It does not

allow exact generalization to any population, since the sample was in no sense random.

Further research should extend these findings to chemical exposures. The few chemical tests given in this study produced results similar to foods. If the results are replicated for insecticides and pesticides, rather serious implications for our present methods of growing food could result. The clinical ecologists find no difference between reactivity to foods and to chemicals in their clinical practice.

The MMPI may need careful examination if cerebral allergy is established as fairly common among the mentally ill. For example, several standard cases are presented in Appendix G (Hathaway & Meehl, 1951). Underlined are possible allergy-related symptoms. In the first case, the psychologist claims the patient "had poor insight into the possible psychological background of his problems." It could equally well be argued that the psychologist had poor insight into the possible allergic background of the patient's problems. There is a need to explore among patients with cerebral allergy any identifying pattern on the MMPI which would differentiate them from other patients.

If nothing else, this research has opened the door for further research into the possible allergic causation of some psychological disorders. Funding for such research is essential, in spite of its "unorthodox" approach to mental

illness. The theories and findings of the clinical ecologists can no longer be dismissed or ridiculed as without merit or relevance to the fields of medicine and psychology.

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APPENDIX A

CASE HISTORY OF C.S.

C.S. is a ten year old girl who was under treatment for asthma, hay fever and stinging insect hypersensitivity. Chemical susceptibility was suspected when she became ill in school shortly after a freshly printed paper (Ditto process) was given to her at school. She recalled that the paper has a strong odor and the print was not quite dry when she received it. She became nauseous and dizzy immediately and within a few minutes had a moderately severe headache and was unable to concentrate on her lesson. She often had these symptoms in the main office when the duplicator was in operation; the solvent in the ink was methyl alcohol.

Her first ethanol test for chemical susceptibility was given intracutaneously by Randolph's original technique which employed two doses of 0.025 cc about one inch apart; the concentration was 1:250 because the diagnosis was strongly suspected and a weaker dose was used. As in all provocative tests, the identity of the test solution was not known to the patient and no suggestions were made regarding results of the examiner's expectations.

She became tired, was unable to concentrate and mentioned visual blurring. She was unable to stand without support, developed nausea, chills, a dry throat and said that she felt like she was on a cloud and everything was too bright to look at. A glass of water was given to relieve her dry throat and she complained that it was hot and tasted like coffee; she did not know what day it was and could not recall the names of office staff members who she had known for years.

As the reaction to ethanol progressed, she became restless, overenthusiastic about minor occurrences and then showed considerable irritability. She was unable to read and after looking at the window stated that it was raining very hard; the day was a very bright and sunny one. She decided to telephone her mother who was in the next room at the time but she was incapable of dialing the entire sequence of numbers; her movements were erratic and she could not sustain her interest long enough to complete this simple task. She took a paper towel and said it was a pizza with

pepperoni and promptly ate several pieces before dozing briefly. When she opened her eyes suddenly she realized who she was and where she was and complained of dizziness and abdominal pain; she was slightly hyperactive and became silly. A neutralizing dose of ethanol was given (0.05 cc of 1:30,000) and she was normal within fifteen minutes. She recalled the test reactions as being the happenings of a dream.

A few weeks later she was exposed to the fumes of an antiseptic-deodorant cleaning solution containing pine oil in the girls' lavatory at school and became severely confused and disoriented. She staggered back to her classroom and walked into the wall; she did not know who she was or where she was and she did not recognize her teacher or her mother who was promptly sommoned to school. The school authorities were equally divided in their interpretation of this chemical reaction; several observers were certain that she was psychotic and the others suspected that she had taken some drug in the girls' bathroom.

The patient was hyperactive and disoriented when she arrived at the author's office with her thoroughly frightened mother. Fortunately, the author had made the diagnosis of cerebral hypersensitivity to petrochemicals and after a period of observation lasting well over an hour (in the presence of two physicians who were visiting the office), she was given her neutralizing dose as established on the previous visit and promptly cleared. The author obtained handwriting samples and drawings at the time of her reaction. There is absolutely no doubt in the writer's mind that in any other office, with a few rare exceptions, this child would have been given a sedative or a tranquilizer and observed for a while before transferring her to a psychiatric hospital. Surely a tragedy was prevented in this situation which could have been completely mismanaged because chemical susceptibility and cerebral "allergy" are not widely accepted as clinical entities. It was decided to try to obtain a permanent record of this type of reaction and without the patient's knowledge of the purpose of the visit she was seen several weeks later for another ethanol test with tape recording facilities and a motion picture camera.

The same provoking dose was employed and she had a reaction that was allowed to continue for three hours before it was terminated by neutralization; two witnesses were present throughout the entire visit. Tables I and II are reproductions of a tree and the alphabet which were drawn during the course of her reaction; she was asked to draw a nice tree and to print the alphabet from A to Z in neat

capital letters of the same size as carefully as possible. The tree drawing was shown to a clinical psychologist, Dr. F. Winer, who stated that it was the work of a schizophrenic individual; he also commented on Table III indicating that this appeared to be the work of a happy well-organized individual. Tables III and IV were produced twenty minutes after she was given her neutralizing dose of ethanol; control/recovery alphabet was by error, drawn with a permanent type felt marking "pen" and as she was completing the last few letters she became uncomfortable, irritable, confused and developed facial flushing from the toluene solvent in the marker. (On subsequent office visits it was learned that she always was uncomfortable in school when permanent marking pens were in use, and on one occasion while she was preparing a poster for her art class she suddenly began to rapidly draw disfiguring lines in all directions which ruined all of her previous carefully executed work. This acute cerebral reaction was interpreted as a voluntary act performed by an abnormal child.) The peculiar hieroglyphic-like symbols of Table II provide an excellent example of the type of cerebral dysfunction that can result in a chemical neuroallergy; she was absolutely certain that she was printing the alphabet.

As the reaction progressed, many of the previously evoked symptoms appeared again. For a while she regressed to infantile behavior with screaming and she attempted to bite her mother who she thought was a male teacher whose class she had been in two years ago. Her mother's green sweater was described as the man's orange jacket and her white blouse was the man's blue shirt. She was not able to correctly identify any of the colors of a group of wooden beads and she saw purple spots floating on a yellow background. The patient was unable to spell three-letter words; she loudly replied to the request for the spelling of "cat" with "gip", pig spelled in reverse, and pronounced each letter with great zest. When asked to slowly count from one to ten she got the numbers out of sequence and after giving a few numbers she began to add letters of the alphabet and mixed numbers and letters in a disorganized fashion with considerable enthusiasm. She did not remember where she lived and was unable to correctly describe any room in her home. If she was not addressed by her middle name, which was never used, she became hysterical and refused to cooperate; there were mood swings from silliness to mild depression and brief periods of increased motor activity where it was impossible for her to remain in one place. She fearlessly and compulsively performed a series of somersaults on a small couch and when she tumbled forward she stated that she was going backward and vice versa. She struck her elbow against the wall while tumbling and peevishly complained at

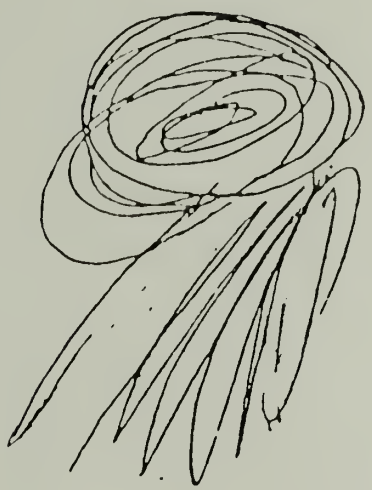
great length about the injury to her knee. Her thirst was not satisfied by cold water because she insisted that she had been given hot Coca Cola.

She was unable to read a comic book aloud, and in the manner of one who is just learning how to read, she made up a childish story which she pretended to be reading. She played with some pieces of office equipment and had a grand time breaking tongue depressors which she threw up into the air and exclaimed that it was snowing; the stethoscope was the thing that her mother played music on at night but this one was broken and should be discarded. There was a joyful period of drawing on her palms with water-base markers which she later identified as carrots that were cooked on the stove (floor) along with peas (cotton balls), tomatoes (flashlight bulbs) and matches (tongue depressors). She satisfied her hunger with pieces of paper which she identified as lettuce and hot dogs. Her eyes crossed briefly and she had a chill which she tried to relieve by manipulating a wall lamp that was burning; the lamp was cold and she became angry because handling the light did not turn on the oil burner and provide heat for her chilly state. There was much infantile indignation which persisted for approximately twenty minutes after the neutralizing dose of ethanol was given; she had received hundreds of injections in the past without any complaint whatsoever. The author was addressed as Uncle Paul who had just stuck a pin in her and she would not play with his dumb children any more because of his mean treatment.

About twenty minutes after the relieving dose was given the patient suddenly came out of her reaction and hugged her mother. She had complete amnesia for the entire experience but remembered that she had had some injections and had become sleepy. It was learned that she had become disoriented while standing next to a car with a running motor and in her confusion had walked directly into the side of the vehicle. When leaving the house for school each day she usually felt quite dizzy and was very unsteady going down the back stairs from the kitchen with its gas range and fumes.

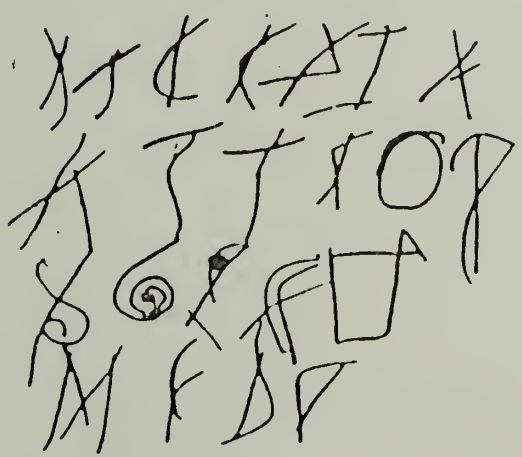
This dramatic clinical evidence secured the complete cooperation of her parents and the home environment was greatly modified by removing many of the sources of in-door chemical air pollutants; the gas appliances were replaced with electric ones and numerous household cleaning and maintenance products which were the source of the volatile chemical incitants were removed. This environmental change was immediately of considerable benefit; her morning dizziness disappeared along with her fatigue and there was a striking improvement in her school performance. In addition, as has

often been noted, there was a very happy development shortly after the natural gas was eliminated from her home—her mother's arthritis of fourteen years' duration disappeared completely, and six months later a provocative test with ethanol elicited a typical attack of this woman's former severe joint pains.

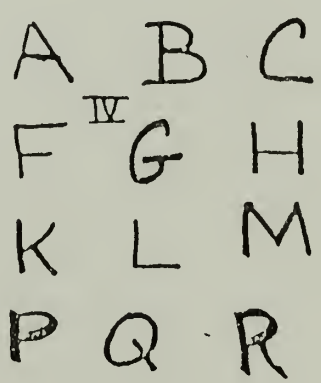


Drawing I Provocation
Ethanol .05cc 1:250

Drawing III Neutralization
Ethanol .05cc 1:30,000



Drawing II Provocation



Drawing IV Neutralization

Source: Mandell, M. (1973), pp. 84-86.

A P P E N D I X B

THE CASE OF L

The physicians treating him felt compelled to conclude that L's asthma must be psychological. Of late, his attacks had begun, without apparent reason, to become more frequent and more severe. Heavy doses of steroids failed to control the symptoms. Extensive physical examinations had repeatedly failed to turn up anything that would explain why this 12-year-old boy, who had initially done so well at the Children's Asthma Research Institute and Hospital (CARIH), had suddenly begun to slide downhill. Could it be that the anxiety and depression that had begun at just about the time his asthma had gotten worse were triggering the attacks? And could these, in turn, be because of the fact that L. was soon to be discharged to return hom? These possibilities were given weight by nurses' reports that L. had lately appeared to "enjoy" being admitted to the hospital emergency room. And, clearly, his despondency did seem to correlate with the severity of his asthma.

Psychotherapy was initiated to explore the presumed contributions of emotional factors to L's condition, but revealed nothing conclusive. It seemed to his therapist that L's depression and withdrawal were more the product of discouragement over the failure of medication to control his symptoms, and his acute embarrassment over the effects corticosteroid drugs had on his appearance, than the reverse. Nevertheless, the hypothesis that L's asthma was emotionally induced, or perhaps even voluntarily brought on, was not easily rejected. For example, L. reported to his therapist, on the occasion of one severe attack, that he was relieved to be in the hospital and out of his cottage, because trouble had been brewing with the other boys.

The solution, when it finally came, was unexpectedly simple. L. had been, as mentioned, observed to be withdrawing more and more from social activities. He was spending a large part of his time in solitary pursuits. One of these pursuits, building models, he seemed particularly to enjoy. Since he had started spending time this way, L. had suspected that the smell of the glue he was using might be irritating his throat and lungs. However, he never mentioned this fact

because he enjoyed building models and was afraid he might be stopped. Nor could he give up his hobby voluntarily. Thus, a vicious cycle had been in process. Model building aggravated L's asthma which, in turn, required him to spend more time alone, that is, building models.

With this discovery, a nonodorous glue was obtained for L. to use. His attacks subsided and his good spirits revived. At the latest follow-up since his discharge, L. is reported to be doing quite well at home.

Source: Purcell & Weiss (1970), p. 602.

APPENDIX C

THE PLACEBO EFFECT IN MEDICINE, PSYCHOTHERAPY, AND THE LABORATORY: A CRITICAL REVIEW

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This paper is intended to critically review the literature on the placebo across medical, psychotherapeutic, and laboratory environments, and to provide a model of placebo reactions with heuristic usefulness in prediction. First, a historical backdrop is provided, followed by a discussion of definitional problems.

History

The placebo phenomenon is not new, but only within the past quarter-century has it become an object of careful scrutiny. Shapiro (1960) reports only 21 articles on the subject between 1900 and 1954, while 35 additional ones appeared in the succeeding four years alone. Although no compiled data are available beyond 1957, a cursory review of the literature shows that this upward trend has continued. In terms of the authors of the articles, Shapiro found this trend to be true both for psychiatrists and psychologists as well as those not in these fields. Certainly, the advent of modern double-blind methodology has contributed to the frequency of studies employing placebos, as well as spurring interest in the study of placebo effects per se. Although Honigfeld (1964a) points out that the double-blind methodology is not new, dating at least back to 1908, it was certainly not common until more recently.

Placebos have played a prominent role in treatment historically, especially before the twentieth century. Honigfeld mentions that except for the past 80 or 90 years, the history of medicine has largely been a history of the placebo effect. Many remedies were non-specific in use, such as bleeding, cupping and leeching. Honigfeld marks the beginning of specific treatment with von Sydenham, who demonstrated the efficacy of quinine in treating fevers of malarial origin, although Shapiro (1971) disputes the true identity of the discoverer.

Shapiro (1960) has written an excellent review of the role of the placebo effect in history, containing many interesting anecdotes. For example, Hippocrates included no treatment of specific value in his medical repertoire. Remedies used by other physicians in ancient times included "'flesh of vipers, the spermatic fluid of frogs, horns of deer, animal excretions, holy oil'" (p. 219). The lungs of the fox were given to consumptives since the fox was long-winded, and the fat of the bear was given to the bald since the bear was hirsute. In spite of such apparently ineffective measures, the physician remained in an honored place within society, a fate which Shapiro attributes to the power of the placebo rather than the strength of the medication. The argument that the high standing of healers throughout history proves the power of the placebo is fallacious, since people have long believed in techniques that we now know could not possibly have afforded relief for certain types of problems. For example, people have used rain dances to induce rain, a procedure with no effect on the external world. If the rain dance caused the dancers to believe rain had occurred, this would indeed be a placebo technique, but more likely the technique is best classified as a superstitious behavior. Likewise, it could very well be that, contrary to Shapiro's interpretation, the physician afforded no relief but remained in high standing, not because of specific or placebo healing power, but because of the necessity for his role. The shaman or medicine man may not be open to this criticism, because when one is treating human ailments rather than attempting to effect external physical events, perceived or real effects cannot be ruled out. In other words, widespread and lengthy acceptance may not necessarily be proof of efficacy, but only of need.

A striking illustration of placebo effects in more recent times is provided.

> A Dr. Raymond at the Salpetriere in Paris found 70 percent of patients suffering from a variety of diseases, including tabes, were treated successfully by suspending them by their feet, causing the blood to flow into their heads. A collaborator of Bernheim at Nancy, a Dr. Haushalter, reversed the procedure and suspended the patient's head upwards and obtained a similar percent success in a variety of organic and nervous diseases. (p. 221)

That placebo treatment need not always be wholly successful is attested to by the following account of the case of Charles II.

> "A pint of blood was extracted from his right arm, and a half-pint from his left shoulder, followed by an emetic, two physics, and an enema comprising fifteen substances; the royal head was then shaved and a blister raised; then a sneezing powder, more emetics, and bleeding, soothing potions, a plaster of pitch and pigeon dung on his feet, potions containing ten different substances, chiefly herbs, finally forty drops of extract of human skull, and the application of bezoar stone; after which his majesty died." (Van Dyke, in Shapiro, 1960)

Just as physicians have knowingly or unknowingly administered placebo potions, poultices and pills in the past for physical illnesses, so too have they attempted to correct mental and emotional disorders by similar means. Prehistoric man used trephining to allow the escape of evil spirits, a rather drastic solution. Galen estimated that 60% of his patients suffered from complaints of emotional rather than physical origin, remarkably similar to the modern estimate of 50-80% (Shapiro, 1971). Presumably his treatment of these patients was no more enlightened than of his physically ill patients. In more recent times, Rachman (1971) has discussed the history of the insulin coma therapy to cure schizophrenia. This therapy was quite popular and was in widespread use up until the late 1950's. It was especially recommended for acute cases and was reputed to result in remissions of better quality than any other means of treatment. But then the method fell into disrepute. As Rachman summarizes it, "in the space of a mere 14 years—1949 to 1963—it changed from being a revolutionizing treatment to one which did not even merit description in a standard textbook" (p. 2). Of course, it is not known whether the schizophrenic actually improved initially, or whether improvement noted was due to biased perceptions and ratings of researchers. The former only would be classified as a placebo effect. Thirty-nine of 48 schizophrenics were also found to improve over six months during frequent base-rate interviews before the experimental manipulation was introduced (Honigfeld, 1964b).

In reviewing treatments similar to insulin shock therapy, Honigfeld concluded "History reveals the introduction of new therapies is characterized by great enthusiasm. It generally requires a number of years for the sobering influence of repeated and undramatic failures to make itself felt." An often cited principle of the nineteenth century medical profession was "Use the new drugs quickly, while they still have the power to heal."

Definition of Placebo and Placebo Effect

What is included in the term placebo, and what is excluded? The word is derived from the Latin "placere" meaning "to please" (Shapiro, 1971). And, the placebo has often been administered to please, as attested to by the endurance and proliferation of seemingly ineffective and worthless treatments throughout history. In the medical sense, which is the narrowest use of the term, the placebo is usually inert medication given for a presumably physical complaint.

Fischer and Dlin define the placebo as "'the agent employed with or without some ritual, but always with the suggestion or implication of its power or helpful properties'" (Kurland, 1960). This certainly captures the role of the physician in dispensing placebos, but fails to distinguish, for example, between active and effective drugs from those pharmacologically inert. They continue their definition by labeling the placebo reaction as "The physiologic and psychologic reaction to the administration and acceptance of the placebo . . .", which may be positive or negative. Thus, the placebo may benefit, have no effect on, or even impair the recovery of the recipient.

Gaddum (in Beecher, 1955) has viewed the placebo in slightly different perspective, that of the experimentalist attempting to clarify the effects of drugs. "A placebo is something intended to act through a psychological mechanism. It is an aid to therapeutic suggestion, but the effect which it produces is either psychological or physical. . . . They have two real functions, one of which is to distinguish pharmacological effects from the effects of suggestion, and the other is to obtain an unbiased assessment of the result of the experiment."

The assumption of intent rules out the historically most common type of what is more broadly called placebo. Most placebos began as substances or techniques believed to be efficacious in the treatment of disorders, and only later have they been discovered to be pharmacologically ineffective or inert. This omission, combined with the limitation to experimental use, seems to be excessively narrow.

Honigfeld (1964a) has more broadly defined the placebo effect as "any effect of medical intervention which cannot be attributed to the specific action of the drug or treatment given." Thus, any effect on the recipient due to the attention, concern or other such factors accompanying

treatment is a placebo effect, since it is not specific to the particular drug or treatment employed. An important problem with this definition is that the placebo can be credited with effects due to factors irrelevant to the placebo situation. Thus, an ulcer that clears up following the administration of placebo therapy, may have disappeared without therapy. In terms of neurotic symptoms, H.J. Eysenck has labeled this spontaneous remission, and this type of factor represents something quite different than what is generally meant by the term placebo. In order to clearly distinguish these groups, and to avoid misinterpreting the strict meaning of Honigfeld's definition, a sound amendment to the definition would be to add the phrase "but can be attributed to non-specific factors of the intervention."

Up to this point, in defining the term placebo, we have been focusing on the medical sense of the word. These placebos may be medication, surgery, or other forms, but in all such treatments a psychological mechanism is evoked which operates on a physical problem, presumably by emotional or psychosomatic mediation. But can the definition be expanded to include non-medical treatments such as for purely emotional or mental disorders? There would appear to be a problem here, because now elements of psychotherapy may be viewed as placebos, if their effects are non-specific. While placebos in the medical sense involve a psychological mechanism to treat a physical problem, placebos in the psychotherapeutic sense involve a psychological mechanism to treat a psychological disorder. But this is precisely what psychotherapy attempts to do! If all psychotherapy is assumed to be placebo, or all placebos to be psychotherapeutic, both terms would lose their meaning. Are client-centered therapy and systematic desensitization elaborate techniques of verbally administering sugar pills? Or are the sugar pills equivalent to a poor man's psychotherapy? The solution to this apparent dilemma is found in the following considerations. First, in medicine, a placebo may operate on a physical complaint with physical concomitants or it may merely affect the degree to which the patient psychologically suffers. The placebo to the ulcer patient may improve the ulcer or may help the patient bear the discomfort. In the latter sense, even the medical placebo is analogous to the placebo in a psychotherapeutic setting. Few would argue that both senses are not important and valid usages of the word placebo.

Secondly, placebos may be administered in drug form explicitly for emotional and psychological problems. The placebo may be a pill, the target symptom may be anxiety, and the symptom may be relieved by the placebo alone. Few clinicians would wish to label this psychotherapy. It is

only when we speak of placebo therapies, or elements of psychotherapy that are placebos, that the distinction may become fuzzy. What is important in defining the placebo is not its form (which may be pills, surgery, splints, or certain therapies or portions of therapies), but the common mechanism by which it may operate in all these cases. In all cases the recipient is presented with an inert substance or ineffective procedure, and then proceeds to improve. Since the placebo by definition is always inert or ineffective (the recipient must know s/he is being treated) other variables are responsible for the obtained change. It is these other variables that cause the placebo effect, whatever it may be in any given case. Thus, the placebo effect can be viewed as an extraneous or confounded variable producing a result that is non-specific for the theoretical system employed in the treatment. In the medical model, a physician's authoritative air or interest in the patient may spur hope, leading to greater recuperative abilities. In psychotherapy, an extraneous variable like enthusiasm of the therapist may be responsible for the improvement. But this enthusiasm may have no part in the theoretical orientation of the therapist. For example, a school of therapy may claim anxiety can be reduced by imagining pleasant landscapes. If an evaluative study found that the clients did indeed relax when employing this technique, the technique would not be a placebo if the relaxation could be attributed to it. But if the relaxation is due to variables such as confidence or attention, then the cure is a placebo cure. An interesting implication of this position is that, literally, today's placebo may be tomorrow's treatment. If our imaginary theorists incorporated the extraneous variable into their theory, then it is no longer a placebo. If an effect were achieved, but due to non-specific factors, this would be a placebo effect. Once pinned down and harnessed, it is no longer such.

To summarize, the placebo can be seen as operating through a psychological mechanism, the pathways of which we may be unaware, and as the confounding and extraneous factors found in the placebo situation. In either case, identifying the placebo may lead to a new theory incorporating it as a specific factor. In a sense, the placebo effect is a function of being treated rather than any specific treatment. It is not surprising, therefore, that an improvement in neurotic symptoms may be found following an initial informational interview, before the first therapy session (Frank, 1974).

Taking all of these factors into account, probably the best formal definition and the one adhered to for this paper is that of Shapiro (1971):

> A placebo is defined as any therapy, or that component of any therapy that is deliberately used for its non-specific, psychologic, or psychophysiologic effect, or that is used for its presumed specific effect of a patient, symptom, or illness, but which, unknown to patient and therapist, is without specific activity for the condition being treated.

In the following review of placebo studies, medical, psychotherapeutic and laboratory studies will generally not be treated separately. It is the intent of this paper to examine factors common across settings and symptoms in the operation of the placebo, rather than fragment the discussion simply to the level of neurotic anxiety and surgical wound pain. Also, many symptoms are not clearly classified as medical or psychological in origin, such as insomnia. For these reasons, studies will generally be distinguished along these lines only when the flux of variables associated with these settings or type of symptoms seems to differentially affect the placebo effect. The rest of this paper will concern general issues, beginning with placebo-induced pain relief.

One of the oldest and most common uses of the placebo is for the relief of pain. Certainly this symptom served as a focus of the early research on the placebo, found in the medical literature. Lasagna, Mosteller, von Felsinger, and Beecher (1954) compared repeated doses of morphine and placebos in relieving post-operative wound pain. In one study, those who reported pain relief from the placebo tended to obtain greater relief from morphine, although not significantly so. In a second study, the morphine was significantly more effective among those reacting to the placebo. The degree of pain relief afforded by the placebo was assessed in both studies. In the first, 7 of 14 patients reported an average of 50% pain relief for at least one placebo administration. In part 2, those with one dose of placebo received relief 53% of the time, 2 or 3 doses gave relief 40% of the time, and four or more doses gave relief 15% of the time.

There are a number of flaws with this study that may affect interpretation of the data. First, as the authors point out, pharmacological sophistication, or the ability to discriminate between morphine and a placebo is possible since patients received both. This could result in a loss of power for the placebo. Secondly, as Honigfeld (1968) has pointed out, this study and many others fail to incorporate a no-placebo control group. If one wishes to study drug effects, one must have a placebo control. If one wishes to study placebo effects, one must have a no-placebo control.

It is not known what course the pain would have taken if not treated. Thus, it may not be true that the placebo power dwindles with repeated use, but that as pain dwindles, so does the relief afforded by the placebo. There may be ethical dilemmas attached to withholding any treatment whatsoever from those in pain, but problems of interpretation remain without the no-treatment control group.

Beecher, one of the coauthors of the above study, has continued research along these lines (1955, 1959, 1960, 1968). He (1955) discussed the question of whether placebos relieve only "imaginary pain" or whether they can significantly affect pain of physiological origin, and concludes that the latter is possible. In a sampling of 15 studies, Beecher found a remarkably stable pattern for the average relief of symptoms by placebo, 35.2 $\pm$ 2.2%. The constancy of degree of relief afforded seemed to him to be due to a common mechanism operating in all cases. Again, as is true of most studies in this field, the appropriate no-placebo control is lacking. In any case, Beecher interprets the relief of pain afforded by the placebo as being due to what he terms the reaction phase of pain—the non-physiological, interpretative phase of pain. In other words, the significance or meaning of the sensation determines how painful it is perceived to be.

Beecher (1960, 1968) argued that if meaning of pain is important, then differences in effectiveness of the relief of pain between pathological pain and experimentally induced pain could be due to variation in this factor. He reported that in studies of experimental pain (heat, pressure), roughly 3.2% are relieved by placebo. Of course, many other variables are also different in these two situations. For example, while pathological pain may be chronic and low level, experimental pain may be acute and intense (shocks). Nevertheless, the hypothesis is reasonable. The patient may see his pain as meaning injury or disease, while the subject may perceive his pain as lacking these meanings. Orne and Evans (1965) found that subjects would willingly dip their fingers in an "acid" bath, presumably indicating a trust that no harm would befall them. Likewise, in the experimental setting, subjects may trust that the pain does not signify internal damage. This difference in anxiety or stress would mediate a difference in placebo responses, according to Beecher. It is interesting that morphine is also ineffective for experimental pain.

Gruber (1956) reported that when patients in an analgesic receive a placebo dose, they report a sharp increase in pain. Presumably this is due to attributing of equal power to the placebo, with the subsequent explanation that the pain must be greater.

Shipman, Greene, and Laskin (1974) investigated the effect of a placebo therapy on the myofascial pain-dysfunction (MPD) syndrome, which is characterized by diffuse facial pain, muscle tenderness and limited jaw movement. Three previous studies by two of the authors had found successful placebo therapy rates from 30% to 50%. The study obtainining the 30% rate was simply a double-blind study, while the higher rate was obtained in a study in which the placebo was prescribed and highly endorsed by the clinicians.

Several studies have examined the effect of placebo administration on the pain response, much like Lasagna, et al. (1954) and Beecher's work, but now using a normal rather than physically ill population. Gelfand, Ullman, and Krasner (1963) used 62 female nursing students in either a study of the effects of "a combination of drugs on pain tolerance," or a normative study of pain tolerance. Experimental pain was induced by ultrasound applied to the thumb. A placebo pill was administered to the experimental subjects with instruction that it would act as a powerful agent to prevent pain, and that it would act as a tranquilizing agent to allow greater toleration of pain when pain did emerge. Three measures were obtained, time to first report of pain (pain perception), time from the first report of pain until the subject removed her thumb from the apparatus (pain tolerance), and total time from the trial onset to end. It was found that the placebo group did significantly better than the control group on all three measures. The authors note that these results are consistent with Beecher's position for several reasons. Pain tolerance may be an anxiety arousing measure, since increasing amounts of pain are delivered, and the apparatus involved may have been imposing. Since Beecher views the placebo as operating primarily through its anxiety reducing properties, the effects here would be expected to be similar to those in pathological pain cases. The pain threshold result may not be as meaningful (Clark, 1969), and anxiety presumably would not be as influential here. It was found that pain threshold and pain tolerance responses were uncorrelated.

In an attempt to separate physiological and psychological components of the placebo response to radiant heat pain, Clark (1969) used a sensory-decision theory analysis. Before the placebo session subjects were instructed that they were going to ingest an analgesic used for internal pain, and its efficacy would now be determined on external heat stimulation. Subjects filled out a medical checklist which suggested a narcotic was being used. During the experiment, subjects were asked to judge 5 degrees of thermal stimulation into 13 categories, from nothing to extreme

pain. Results showed that for the four stimulus intensity pairs isosensitivity curves appeared identical for both groups. Similarly, no effect on sensitivity to thermal stimulation (d') was found. However, the placebo did significantly increase the subjective criterion of pain, as well as the criterion for "hot", "warm", and "detection". Clark explains these results in terms of the phenomenal experience of pain or the number of neural impulses remaining constant, while the placebo set increased the social cost of a pain response. Thus, response bias or the demand characteristics accounts for withholding of the proper response, and substituting one of a lower magnitude. One problem with this interpretation is that it fails to rule out Beecher's theory of placebo response to pain. It does not adequately distinguish between response bias or "unwillingness to admit to E that pain had been experienced" and Beecher's secondary processes. Thus it may be that sensitivity to painful stimuli has not been altered, but one does not label or experience it as pain. Sensory decision theory says nothing about this type of phenomenal experience. In spite of this, the finding of no direct effect of a placebo on sensitivity to stimuli is interesting and worthwhile. Any "objective" effect of placebos on pain must take place through other mechanisms. Of course, whether this result would generalize to the pathological pain studies by Beecher and Lasagna is an open question.

Evans (1969, 1975) and his colleagues (McGlashan, Evans, and Orne, 1969) have examined placebos, hypnosis, and pain response. All three reports concern the same study in which volunteers from the upper and lower 5% of susceptibility to hypnosis participated in three sessions: a control session, a hypnotic session, and a placebo session. During the placebo session, the subject swallowed an "'experimental pain-killing drug'" that would afford maximum possible pain relief. The experimental induction of pain involved ischemic muscle pain produced by a sphygmomanometer cuff. The subject also pumped a bulb to displace water in time to a metronome beat. Measures included time and volume pumped to pain threshold and to tolerance. Subjects also estimated subjective pain intensity after each trial. In the control condition, and about 45 minutes after the placebo administration, subjects took a measure of situational anxiety and a check list of psychosomatic symptoms. A significant increase in the placebo condition was found for pain threshold and tolerance (both in time and volume), situational anxiety and psychosomatic symptoms. No effect was found for subjective pain intensity, or estimated water pumped. So subjects experienced an increase in anxiety while performing better on all objective measures in the placebo condition. Unfortunately, the order of

placebo and conditions were not counterbalanced, so practice effects cannot be ruled out, in spite of the lack of an order effect found by Clark (1969). It is possible that the increase in anxiety, perhaps due to the nature of the task, prevented a subjective decrease in pain from appearing, in line with Beecher's hypothesis of anxiety and pain. This may be the most parsimonious explanation of objective changes appearing without subjective concomitant.

One problem with interpreting the pain tolerance results in this study is that, according to McGlashan, et al., subjects continued to press the bulb until their muscle would no longer respond, and were able to endure greater pain. The validity of this measure of pain tolerance is thus open to question.

Evans (1975) reviewed several studies of placebo pain relief to obtain average efficiency ratios (ratio of placebo relief to drug relief). Reviewing seven studies that compared a placebo to morphine, the efficiency ratio was .56. Averaging 10 studies comparing a placebo to aspirin revealed an identical ratio of .54. Likewise, Darvon and a placebo yielded an efficiency ratio of .56. So the effectiveness of the placebo in double-blind settings was a direct function of the strength of the active agent.

Anxiety

The folklore about the role of anxiety in placebo responses is that high anxiety is generally best for the responses. It is assumed that the placebo results in a lessening of this anxiety and this action causes concomitant changes in other symptoms, such as pain perception. This theory is not implausible; even morphine is only effective when anxiety is present (Barber, 1970). When a person is not anxious about a stimulus, he will show a smaller change in GSR to its presentation than if he were anxious (Barber, 1970). Anxious psychiatric patients were found to have lower thresholds for pain than normals or depressed patients (Clark, 1969). Thus, it would be reasonable to hypothesize that if a placebo lowered anxiety about a painful stimulus, smaller autonomic changes would accompany its occurrence. Beecher (1955, 1960) argued that placebos are most effective when the stress (anxiety or pain, for example) is greatest, and cites a study by Cleghorn showing greater adrenal reactivity to a placebo when under greater stress. Several sources cite hysteria as an example of a non-anxious, suggestible state in which placebos are relatively ineffective (Honigfeld, 1960b; Shapiro,

1960). Similarly, Shapiro, et al. (1968) reported on absence of anxiety in their neutral placebo reactors. Singerman, et al. (in press) found high and moderate anxiety subjects tended to exhibit placebo effects more than low anxiety subjects.

Anomalous findings have also appeared in the literature. Rickels and Downing (1967) found significantly better improvement for low anxiety placebo treated neurotic patients. Drugs were most effective at moderate anxiety levels. However, no control for spontaneous recovery was included, and possibly low anxiety subjects simply recovered more quickly. Shipman, Greene and Laskin (1974) found that mild anxiety patients responded best to their placebo therapy. Nisbett and Schachter (1966) studied the misattribution of arousal states from the fear of shock to a placebo pill. Subjects received either high fear or low fear instructions. High fear subjects were less responsive than low fear pill subjects to withstanding pain, but this could have been due to a non-credible attribution in the high fear condition.

An important distinction should be drawn between state (current or situational) and trait (chronic) anxiety (Evans, 1975). The concept of state anxiety probably best reflects the theorizing and results in this field. Surgical patients, neurotics seeking initial help and college students about to be shocked could all be in a situation arousing state anxiety. Shipman, et al. (1974), the strongest contrary study, assessed anxiety by means of MMPI scales, which are intended to assess trait anxiety. Frank (1974) failed to find a relation between placebo response and autonomic functioning, although the nature of the tests was unclear. Presumably, he was assessing trait autonomic functioning rather than state anxiety. Current anxiety has been found a better predictor of placebo response than chronic anxiety (Shapiro, Mike, Barten & Shapiro, 1973). Research thus seems to indicate that moderate or high state anxiety, and perhaps low trait anxiety, best contribute to a placebo reaction. This finding is consistent across the medical and psychoterapeutic literature. One study in the misattribution field which examined the issue of the effect of state anxiety, found low and medium anxiety subjects got a placebo reaction, while high anxiety subjects got a reverse placebo reaction (Zuckerman, 1974). These findings were post hoc, but perhaps the impact of the dentist's office was great enough that even the low anxiety subjects were "anxious", and the high anxiety subjects reached a point where placebos were ineffective or even harmful.

An interesting question can be raised concerning the generality of the term anxiety as employed here. Would

these findings also apply to other forms of state anxiety, such as evaluation apprehension? Or must the anxiety be directly related to the symptom treated by the placebo, as in pain, shock and insomnia studies? To reformulate the issues, is the role of the anxiety that of providing generalized energy to fuel placebo reactions, or must the anxiety be specifically related to the treated symptom? The misattribution literature has addressed a related question, but not in the sense intended here. For example, suppose depressed patients were given placebos to lift their spirits. Would it make any difference in terms of placebo efficacy if some were under conditions producing evaluation apprehension in regard to an unrelated task and some were not? Note that depression is not being misattributed as to its cause.

Placebo Effects in Controlled Settings

An important set of issues in the placebo literature is the objective changes induced by the agent as well as subjective effects. Laboratory studies using normal rather than pathological subjects have attempted to ascertain the parameters of the placebo effect and to isolate its components. These studies have generally followed the medical and psychotherapeutic interest in the phenomena. Several studies have examined both subjective and objective change to a placebo.

Brodeur (1965) studied the effects of stimulant and tranquilizer placebos on 45 healthy advanced pharmacy students. Most of the subjects were male. Both subjective and objective measures of placebo effects were obtained. The subjective measures consisted of an adjective checklist previously found to differentiate between stimulants and tranquilizers. Pulse rate served as an objective index of placebo effects. The study took place within the context of a pharmacy laboratory exercise, a regular event in which students carried out routine tasks. Subjects were given the placebo, with instructions congruent with the stimulant, tranquilizer or control group to which they had been assigned. Although the ordering of groups was as expected on the checklist scores, analysis of covariance showed no significant differences among groups on this measure.

In terms of the pulse rate measures, results were generally congruent with instructions, with an analysis of covariance showing significant differences between the groups. It was found that the stimulant and tranquilizer groups differed significantly. A methodological flaw concerning

the pulse rate data was that subjects took each other's pulses, and knew to which group their partners were assigned. Introspective reports showed that 60% of the subjects reported feeling the expected effect; 73% in the stimulant group and 47% in the tranquilizer group. Whether this difference is significant was not reported. Although no effect was observed for check list data as has occurred for real stimulants and tranquilizers, global self-reports and pulse rate data concur in the placebo having some effect. Other interpretations of these data are possible.

Two related studies of the effect of placebos versus drugs on mood and task performance were performed by Ross, Krugman, Lyerly and Clyde (1962) and Lyerly, Ross, Krugman and Clyde (1964). In the earlier study, a test was made of these factors by crossing two key variables: drug/no drug and pill/no pill. Thus, it was possible to compare drug informed subjects, disquised drug subjects, placebo subjects and control subjects who received no pill and no drug. The pill subjects (drug and placebo) were told the study involved the effect of the drug on mood and eye-hand coordination. The no-pill groups (disguised drug and control) were told the study concerned the mood of an older person and eye-hand coordination. The Clyde Mood Scale was administered after an hour, along with a tapping task and a crossing the H task. Although no significance levels are reported, the authors report a tendency for the drug groups to exhibit an impaired performance on the tasks and to be less comfortable in mood. It was found that the disguised drug group showed the greatest impairment on the tasks and reported the most discomfort on the mood scales. Although not discussed by the authors, this group is of interest because they are the opposite of the placebo group. While the placebo group received "nothing" and expected "something", this group received "something" and expected "nothing". On this basis, it would be expected that the placebo group would do quite differently than this group, and such is the case for the mood scale. The placebo group reported the greatest comfort, although no test for significance was reported. A Friedman analysis of variance did find significant differences among the groups on the mood variables and motor tasks, but no cell comparisons were reported. Still, it can be inferred that the placebo group was significantly more comfortable than the disguised drug group, but it is not known if the placebo group differs from the control group. The placebo group did not differ from the control group on the motor tasks.

In the second study, the design was expanded to include a sedative. Here, amphetamine, chloral hydrate or a placebo was administered, crossed with stimulant,

sedative or no effect instructions. Procedures and tests were similar to the first study. On the motor tasks, it is reported that the amphetamine instructed placebo subjects showed impairment as compared to the control group, but no significance level was reported. The chloral hydrate placebo subjects generally performed at the same level as the control group. On one task, it was found that amphetamine-instructed placebo subjects performed significantly worse than the amphetamine subjects (either capsule or disguised), who also did worse than the control group. This was a measure of the time taken to complete the mood scale, and the chloral hydrate placebo group took significantly less time than the amphetamine placebo group. This paradoxical finding may be an example of the reverse placebo effect, in which effects opposite to those instructed appear for placebo subjects. This topic will be discussed at greater length below. Unfortunately, no comparison on the chloral hydrate instructed placebo group and the control group on this task is reported, although the trend is in the direction of faster time for the sedative instructed placebo group. It was found that this measure discriminated many groups from each other, a fact which the authors attribute to the instructions to "work at your own pace." All other tasks were done as rapidly as possible, and may have shown the ability of subjects to compensate for drug effects. A second consideration not mentioned was that this was also the only task in which unobtrusive measures were obtained. Subjects were not aware of being timed. This makes any reverse placebo effect even more interesting since subjects were presumably not aware of a demand on them. Perhaps the best explanation is that while the drug subjects compensated, the placebo subjects in effect over-compensated for expected but non-existent drug effects.

Mood scale scores were analyzed separately for the two drug groups. The mood scale analysis showed that the disguised drug groups did not differ from each other. This finding, combined with the ineffectiveness of chloral hydrate in any form to produce an effect leads to the conclusion that either the scales were not sensitive, or the dose of chloral hydrate was so small as to function as a placebo or both. In any case, the chloral hydrate placebo had no effect on reported mood, and while a significant main effect for receiving amphetamine and for receiving a pill were found, the interaction was not significsnt. Because of the lack of planned comparisons it is difficult to tell the exact effect of the placebos on the mood scores. The authors claim greater comfort for the placebo groups than the controls, but do not provide the necessary data to document this claim. To summarize, the chloral hydrate drug manipulation was not sufficiently strong to have an impact, and

the placebo cell is not compared directly with other cells to isolate its effect. One task of four did show significant differences for at lease one placebo group from the control group. Where comfort declined for drug subjects in the first study, this effect was reversed in the second study, and while placebos affected mood more than tasks in the first study, they may have reversed this trend in the second.

Using a geriatric population, Nash and Zimring (1969) examined expectations of drug effect and openness to experience as predictors of placebo response on several short term memory measures. Expectation was significantly correlated both with short term memory improvements and experienced change. Initial performance on the short term memory tests was the same for both high and low expectation groups.

To summarize, it was generally found that the placebo had no effect on fast reaction motor tasks, such as crossing "H's" and tapping times (Lehman & Knight, 1960; Ross, et al., 1962; Lyerly, et al., 1964; Buckalew, 1972). It may be that these results can best be viewed as a motivational ceiling effect, to be discussed more fully below. Other dependent variables did show significant effects both objective and subjective, but must be considered tentative because of methodological and statistical flaws and omissions. Further, better controlled laboratory studies certainly would be appropriate.

Misattribution and the Placebo Effect

At this point, the research on misattribution will be discussed since much current research on placebo effects at least pays obeisance to attribution theory. The fundamental premise of attribution theory as applied to placebo effects is that the phenomena may be a misattribution process, in which the actor attributes the cause of arousal or fear or bodily symptoms to a neutral cue rather than the true source. For example, a person may attribute his fear in a shock experiment to a placebo rather than to the shock itself, and this attribution may affect future behavior. Theorists have argued that such misattributions can cause better sleep, less fear of shock, and better tolerance of dental pain. Relevant studies in this category will be briefly reviewed, covering studies that occur in the laboratory and the field and that are both theoretical and applied in orientation.

Probably the seminal study in this field was Schachter and Singer (1962), who found that subjects could be induced to label their adrenaline-caused arousal as either anger or mirth, depending on situational cues provided by a confederate. The effects can be viewed as misattribution with real consequences, since subjects correctly interpreting their arousal (Epinephrine Informed) showed little affect, behaviorally or via self-report. Much like Lyerly, et al. (1964) and Ross, et al. (1962), these subjects who surreptitiously received a drug must find other explanations for their arousal. Schachter's placebo group is of little interest, since they were instructed to expect mild visual effects. One experimental group, the epinephrine misinformed group, was told to expect what were actually irrelevant side-effects, such as numbness, itching and headache. Perhaps such a manipulation can be conceptualized as an active placebo—an active agent is given, but with specific effects quite different from those instructed. It is of interest that these subjects did not experience many of the instructed effects in spite of receiving epinephrine—apparently the arousal is not infinitely plastic in terms of subjective effects. Of course, some researchers (Fehr & Stern, 1970) argue that epinephrine is not just a general arousal agent but tends to arouse fear-like sensations more than the more positive emotions. Another explanation for the failure to obtain placebo effects in this group may be that the subjects were kept busy, whereas in many placebo situations subjects do nothing or engage in menial tasks, at least for a period of time.

Schachter argues that subjects correctly attributing their arousal to the drug will not experience emotion. Instead, they will experience "as if" emotion, that is, they would feel as if they were happy or as if they were angry. Hence, they do not experience emotion in emotional situations. The author would disagree with the over-generalization of this statement. It is the author's contention that normal subjects knowingly experiencing arousal due to sympatheticomimetic agents such as ephedrine or adrenaline, may in a novel or rapidly changing emotional situation over-react or experience strong emotions, in spite of this knowledge. In situations where they must take an active role, as opposed to the Schachter and Singer study, they must rely on past feelings in similar settings or risk over-reaction. When confronted with relatively novel situations or one calling for rapid action, the actor may be forced to rely on his feelings, even though he knows they can't be trusted. This hypothesis has not been researched to the writer's knowledge.

Nisbett and Schachter (1966) attempted to extend the misattribution of arousal states from drug-induced ones

to situationally-induced ones. The theory here is that to the extent that a person is convinced that his shock produced symptoms are due to an outside agent, such as a drug, he should tolerate more shock and experience less pain. Merely attributing discomfort to a drug, of course, may lessen pain attributed to shock, but does not necessarily lessen the total perceived discomfort. An overdose of alcohol can be quite unpleasant, although one is well aware of the source of the discomfort. Implied by the theorists is that the lessening of pain is due to cognitive and situational factors, although the possible mechanisms are not clearly explained. A curvilinear relation between degree of arousal or pain and its attribution to a neutral source is postulated, such that the greatest attribution would take place between no arousal and extreme arousal, in which such an attribution could not be made credible compared to the very salient true source of arousal.

Subjects were led to expect either fear symptoms or irrelevant symptoms to a placebo, and received either high or low fear instructions regarding the painfulness of those shocked to be administered. It was found that low fear pill attribution subjects attributed the shock symptoms to the placebo significantly more than the low fear shock attribution subjects. In the high fear condition, almost all subjects attributed their fear to shock. It was found that the pill attribution in the low fear condition led to this group tolerating significantly more shocks than the low fear shock attribution group. It was also found that the low fear pill attribution group reported significantly less pain than any other group. The criticism can be made that Schachter and Nisbett failed to control for the contiguity of administration of the placebo and the onset of arousal (Weiner and Hooper, 1972). Thus, it could be that the high fear condition would have obtained different results if the placebo was administered before shock was mentioned.

Behrendt, O'Neal and Morris (1974) studied the effect of various types of placebos on shocks given to a confederate. Subjects were given one of four types of placebo: stimulant, tranquilizer, analgesic, or reflex-inhibitor. A "vitamin" was given to the control group. No effect was found due to the placebo manipulation, but two major criticisms may account for the negative results. The placebo manipulation was very weak, and, a number of questionable theoretical links were inserted between the placebo and the dependent measure.

Ross, Rodin and Zimbardo (1969) attempted to further explicate the possibilities of the misattribution model.

They theorize that while the total absence of cognitive cues to explain arousal is rare in reality, it is not uncommon to have two or more such cues in conflict. Thus a cognitive conflict is engendered against a backdrop of "undifferentiated arousal . . . The ambivalent individual searches for a 'correct' and consistent set of cognition about the external world to which he may attribute his internal state, when in fact no such simple causation exists" (p. 280). Subjects were led to attribute fear of shock to either noise or shock. It was found that the shock attribution subjects spent significantly more time working on a puzzle to avoid shock than the noise attribution subjects. This was interpreted as indicating greater experienced fear of shock among the shock attribution subjects. This interpretation has been criticized by Calvert-Boyanowsky and Leventhal (1975).

Davison and Valins (1969) developed the misattribution theorizing a step farther. Arguing that behavior change attributed to oneself will result in maintained change to a greater degree than behavior change attributed to an external agent, such as a drug, they tested their hypothesis in two studies. Methodology was very similar in both studies. Subjects supposedly were taking part in two studies, back to back. In the first, they were to take a "vitamin compound" in order to test its effect on pain sensitivity. Subjects received gradually increasing shocks until they reached their tolerance level. They then took the compound and repeated the shock process, but the experimenter surreptitiously halved the shock levels. Then half the subjects (placebo group) were disabused to the notion that they had received a drug, while the remaining subjects were told the drug was wearing off. Then all subjects participated in a third series of shocks at full strength supposedly for an unrelated study. In general, it was found that the drug/placebo manipulation was successful, so subjects presumably differentially attributed their success on the second trial to the drug or themselves. It was found that the placebo and drug group did not differ on the number of shocks taken on the third shock series before reporting pain. A significant difference was found for pain tolerance for the two groups, the placebo group taking more shocks than the drug group.

An attempt was made to uncover the role of expectations in the third shock series, but unfortunately the measure was obtained post-hoc. A highly significant difference was found, such that placebo subjects reported that they had expected to take more shocks than the drug subjects.

In the second study, a replication was performed with

slight modifications. Pain tolerance level was again significantly different for the two groups, and the percentage of improvement maintained was significant such that the placebo group maintained their improvement more than the drug group. The expectation finding was replicated, since subjects in the placebo group reported that they had expected to take significantly more shocks than the drug group. To summarize the results, there was strong evidence that the placebo subjects endured more shocks on the third series, and some vidence that they were also willing to endure more before labeling the shocks painful. Nisbett and Valins (1972) have viewed the results in terms of hypothesis testing by the subjects. Placebo subjects inferred that they could tolerate shock better after the second series, and disconfirmed the hypothesis in the third series, since they took fewer shocks than in the first series.

Within the theoretical structure of this paper, the "true placebo" group is ambiguous. Certainly all subjects in the second series are serving in a placebo group, believing in a "drug" to reduce pain perception. A placebo effect would result in greater shock tolerance, which did occur, but was not tested for significance. Habituation could also account for greater shock tolerance.

In the third series, the "drug" has worn off for the drug group, while the placebo group perhaps believes that they have some new-found ability to withstand pain. In a sense, this deception could constitute a placebo manipulation. Whether the treatment is the most effective for inducing placebo mechanisms to operate is another question.

Zanna and Cooper (1974) incorporated a placebo manipulation within a dissonance experiment. Subjects were given a pill with one of three possible side effects: tension, relaxation, or no side effect. But no attribution checks were included, to find out how much tension was attributed to the pill and how much to writing an essay, being in an experiment, etc. It was found that subjects in the arousal condition reported feeling significantly more tense than the no side effect condition, while subjects in the relaxed condition reported being less aroused than in no side effect condition. As the experimenters correctly assert, demand characteristics could also account for the obtained data on arousal. Thus, it cannot be ascertained whether or not placebo effects were obtained in this study.

A final laboratory study of misattribution is that of Calvert-Boyanowsky and Leventhal (1975). The authors noted three major flaws of previous misattribution research. First, they fail to prove that misattribution has in fact

occurred. Most studies included no manipulation checks, while the two that did were inadequate or non-comparable across conditions. Second, subjects in the misattribution conditions were usually the only groups to receive lists of arousal symptoms. The one study cited that controlled for this factor found no effect of merely receiving a list of symptoms. Third, accurate expectations were confounded with inaccurate or no expectations.

The researchers then replicated the design of Ross, et al. (1969) with two additional conditions. Subjects were instructed to attribute relevant or irrelevant symptoms to shock in addition to the original two cells of noise attribution. Manipulation checks showed no differential levels of fear across conditions, nor did they differentially attribute their arousal to shocks. Subjects did attribute the cause of their symptoms to 1.5 to 2 causes per cell. Whether arousal symptoms were attributed to noise or shock made no difference in whether the subject worked on the shock or reward puzzle, but subjects given arousal symptoms lists spent significantly less time on the shock puzzle. Since the results of Ross, et al. were replicated and misattribution did not seem to be a factor in the results, arousal information better explains the data obtained.

To determine whether the important factor in the above results was simply receipt of arousal symptoms, or whether the symptoms must be attributed to a plausible source, a second study was carried out. Noise level was manipulated, being either high or low, with the usual shock or noise attribution manipulation. It was found that the low noise subjects instructed to attribute their symptoms to noise worked significantly more than the other three groups on the shock avoidance puzzle. Thus it would seem that the source of arousal symptoms must be plausible. The researchers concluded that arousal symptom information may reduce emotional behavioral responses, but must be within a plausible context. Implausible attribution sources for arousal symptoms result in the highest level of emotional behavior. An important point of this research is that subjects are not as naive or pliable as earlier misattribution research has assumed. They do take several causal factors into account for their symptoms, and discard implausible sources of arousal. In terms of placebo research, causal misattribution could still take place since most placebos are novel and/or ambiguous in their effects. An interesting unresolved question is whether inaccurate information leads to an increase in emotional behavior.

The final section of the misattribution literature review discusses applications of the theory to problems such

as insomnia, speech anxiety and quitting smoking. In these studies, an attempt was made to modify these behaviors by means of placebos and by inducing misattributions.

Storms and Nisbett (1970) studied the effect of placebos on insomniac subjects, who were told they were participating in a study of dream content and internal bodily activity. Placebos were ingested at bedtime to either increase or lower bodily activity. Self-reports of time of going to bed and time of sleep onset were used to deduce length of time before sleeping. Arousal attribution measures showed that the arousal subjects attributed significantly more arousal to the pill than the relaxation subjects. However, differences in reported levels of arousal between pre-experimental and experimental nights were not significant, indicating the placebos had no effect on perceived absolute arousal levels. The effect of the placebos on sleeping was unusual in that a significant reverse placebo effect was obtained. Normal subjects took significantly less time to fall asleep, while relaxation subjects took significantly more. Control subjects reported trivially less time to get to sleep. In spite of these results, subjects reported no change in suffering on experimental nights.

These findings are congruent with the theory of Calvert-Boyanowsky and Leventhal (1975) in that unexpected symptoms in the relaxation condition (arousal) may result in greater arousal and worry. For an understanding of the arousal condition, it may be theorized that the insomniacs suffer from two sources of arousal: physiological and self-produced. Finding oneself in an arousal state at bedtime is expected and may lead to a reduction of secondary (self-produced) arousal.

An attempt to extend the findings of Storms and Nisbett was performed by Kellogg and Baron (1975), again using insomniacs. Replicating Storms and Nisbett closely, they not only found no reverse placebo effect, but actually found a significant placebo effect. Subjects receiving arousal pills took longer to go to sleep (the sedation condition was omitted since it lacked clinical interest). The failure to replicate is made more interesting since a significant rather than non-significant result was obtained. As for the cause for this "aberrant" cell, the authors can provide no compelling explanation congruent with their theory, other than a Type I error. More likely, an unknown variable may be mediating these results, since both reverse placebo effects and placebo effects have been obtained in the past. One possibility is that subjects in this experiment

did not believe in the placebo as strongly as Storms and Nisbett's subjects. Kellogg and Baron report moderately low belief in the placebo, while Storms and Nisbett's subjects attributed arousal to the pill.

A conceptual replication of Kellogg and Baron is Singerman, Borkovec and Baron (in press). Instead of insomniacs, speech anxiety was the target symptom. High and moderate fear of public speaking subjects were assigned to an arousal, sedation or control group.

Self-reports of anxiety were nog significantly different between the arousal and sedation conditions, although in the direction of placebo rather than reverse placebo effects. Analysis of observer ratings also showed few significant differences of interest, while no treatment effect was found for the heart rate data. Post-questionnaire analysis showed that subjects rated their arousal as caused to a significantly greater degree by the speech than to noise bombardment across all conditions. Since the misattribution failed, it is not surprising that subjects generally were not affected by the treatment. The authors plausibly argue that speech anxiety may be too ingrained for subjects to easily misattribute to a noise source.

The effect of the placebo in treating insomnia in a slightly different context was investigated by Steinmark and Borkovec (in press). Four groups were formed—two therapy groups, a pseudo-desensitization placebo therapy group, and a no treatment control group. All subjects indicated they required more than 30 minutes to fall asleep. To counter demand characteristics in the self-report sleep data collected during the experiment, therapy and placebo subjects were informed that no improvement should be expected until the fourth week, when dramatic improvements should begin to appear. The two therapy groups showed significantly more improvement in sleep onset latency during the three week counter-demand period than the placebo and no treatment groups. However, during the fourth week placebo subjects reported a significant improvement as compared to the no treatment group.

The placebo group during the fourth week improved to a point where sleep onset latency was less than one therapy group, although presumably not significantly so. After the fourth week, placebo subjects were offered additional therapy with "'another effective procedure'". All placebo subjects declined, with most of them claiming they no longer had a sleeping problem. In contrast, 11 of 12 no treatment subjects participated in a post-experimental therapy session. Follow-up phone calls five months later revealed no significant change in the reported sleep onset latency of the placebo group.

Ratings of credibility of the various therapies revealed that the placebo therapy was rated between the two active therapies, although they were obtained post-hoc.

Once again, a significant placebo rather than reverse placebo effect was obtained. As for interpretation of the placebo results, there are three possibilities. Placebo effects may be purely a function of demand characteristics (response bias), they may represent a phenomenological change in sleep disturbance, or they may be actual improvements in sleep. The first case seems unlikely to the writer because of the follow-up data and the lack of interest in any further help. The second and third cases cannot be distinguished on the basis of data collected, and both remain plausible explanations.

The misattribution technique has been applied to problems other than insomnia in field settings. An example is Barefoot and Girodo (1972) who attempted to alleviate smoker's withdrawal by misattribution of symptoms to a placebo medication. Dependent measures included self-ratings of anxiety, appetite and difficulty in refraining from smoking, and were assessed at four hours and eight hours. Unfortunately, no manipulation check was included to assess the degree to which the drug could produce symptoms, and the degree to which they attributed withdrawal symptoms to the placebo in the experimental group, as opposed to not smoking. Control and experimental subjects did not differ in self-ratings of anxiety, so apparently the placebo had no effect on anxiety. In terms of perceived difficulty in cessation of smoking, an interaction existed, such that placebo subjects reported significantly less difficulty in the second (later) session, when withdrawal symptoms were more intense for all subjects. Anxiety was a significant predictor of cessation difficulty of control subjects, but was negatively (though not significantly) correlated for experimental subjects.

If Barefoot and Girodo had demonstrated that the symptoms were indeed attributed to the placebo, then the criticisms of Calvert-Boyanowsky and Leventhal would be clearly countered. But since no differential anxiety levels were found, and subjects did report differing ease of giving up smoking, it is plausible that the reason for the greater ease of cessation of smoking in the experimental group was the misattribution of at least a portion of the symptoms to the placebo. Thus, subjects may have experienced the same absolute intensity of symptoms, but have perceived different means to alleviate it, as the authors point out. The control group may have felt smoking would end symptoms, while the experimental group may have believed that to a lesser degree.

Another field application of misattribution methods was Zuckerman (1974), who attempted to ameliorate dental anxiety which was augmented by an injection of adrenaline. Anxiety was assessed before and after drilling, and served as the major dependent variable. Subjects received an anesthetic injection which contained some adrenaline, although neither the dosage nor the effectiveness of the drug is specified. Subjects were either told the injection would lead to a countering of arousal (No Arousal) or to an increase of arousal (Arousal). Control subjects were told nothing. Attribution checks showed that subjects generally attributed their anxiety about equally to the injection and the dental treatment, with no significant differences between cells. These difficulties make the interpretation of other results problematic. One a posteriori finding of interest was that when subjects were broken down into high and low anxiety blocks, it was found that a significant interaction existed such that high anxiety, No Arousal subjects reported more anxiety during the session than the arousal subjects, and low anxiety arousal subjects reported more anxiety during the session than the no arousal subjects. Since no a priori rationale existed for this analysis, it is a shaky finding indeed.

Davison, Tsujimota and Glaros (1973) applied the Davison and Valins technique to insomniacs. After establishing a base line on sleep latenty, all subjects received an optimal dosage of a drug to aid in sleeping. Subjects were informed that they would receive either an optimal or minimal dose, but didn't know to which condition they had been assigned. For seven days they took the night-time medication in conjunction with a psychological relaxation technique. At the end of treatment, the drug was stopped and patients continued the psychological technique. They were told they had received a minimal dose or were told they had received an optimal dose of the drug. Of course, the rationale for this comparison was that minimal dosage subjects would attribute greater power to the psychological technique and optimal dosage subjects would attribute greater power to the drug. According to Davison, et al., the minimal group would attribute the ability to improve to themselves, while the optimal group would attribute it to the drug. Since the minimal dosage subjects felt they would be little impaired when dosage was stopped, they would expect to maintain their improvement. Not surprisingly, it was found that these subjects did maintain their improvement more than the optimal dosage subjects—a straight placebo effect in that what was implicitly suggested was what occurred. There is an interesting twist here, since an active medication was passed off as essentially a placebo, rather than the reverse. The experiment apparently served to increase belief in the efficacy of the relaxation

technique for the minimal dosage subjects. These subjects then may have increased expectations of relief which may account for a placebo reaction during the post-treatment period. A second possibility is that the optimal dosage subjects had a lowered expectation of relief after being informed of the optimal dose they had been receiving, resulting in less expectation for maintenance of improvement, and hence a "negative" placebo reaction.

In summary, the misattribution theory is interesting and pertinent to the placebo problem. Much of the research contains serious methodological omissions and flaws, but in spite of this fact, interesting results have been obtained. Several factors would intuitively seem to operate against strong placebo effects in many of these studies, at least as found in its natural ecology, and these include (1) lack of physically or mentally ill subject population; (2) lack of the usual "help-giving" agent, physician or psychiatrist; (3) use of college students who may systematically differ from the general population, such as in being more critical of psychological research; and (4) implausible sources of arousal change compared with overwhelming known sources of arousal, resulting in a failure to attribute arousal to the desired cue.

In spite of these problems, real placebo effects did emerge (Davison & Valins; Steinmark & Borkovec; Storms & Nisbett; Kellogg & Baron).

Reverse Placebo Effect

The reverse placebo effect can be defined as the occurrence of the opposite of the suggested placebo effect in one subject. Thus must be distinguished from side effects which are merely non-suggested effects. Unfortunately, much of the literature fails to distinguish clearly between these two groups. Certainly, there is no *a priori* reason to assume they are the same and operate through the same mechanism. It also must be distinguished from the usual confounding and sources of artifact in the placebo literature, such as failure to control for the spontaneous rate of the observed symptom.

DiMascio (1968) notes that "paradoxical reactions" often occur to drugs, such that anxious patients may become more anxious on a tranquilizer. Pogge (1963) reports that 4% of a large sample across studies given tranquilizing placebos reported central nervous system stimulation. Only 8% reported central nervous system depression, although Pogge

was reporting only side effects and reverse placebo effects. No base rate was provided, nor were criteria for assessment listed. Since the criteria for an "effect" are arbitrary, percentages are not very helpful.

One of the earliest researchers to report a clear reverse placebo effect was Gruber (1956), in a study of the effects of placebo sleeping medications on hospital patients. These medications were either to impair or aid sleep, and were alternated. Three of 11 patients consistently reported results opposite to the instructions. Since self-reports were used and no control group was included, these results are difficult to interpret.

Fischer and Dlin (1956, in Kurland, 1960) studied placebo effects on three degrees of psychopathology. Negative reactions (which presumably include side effects as well as reverse placebo effects) ranged from 12% to 41% for the groups.

Pichot and Perse (1968) report 19% "negative reactors" to a placebo, a figure which includes both effects negative on several factors as well as side effect occurrences.

Shapiro, Wilensky and Struening (1968) studied the effects of the administration of a placebo on immediate subjective effects as well as to predict clinical course of patients who were normal candidates for psychochemotherapy. The placebo was given to 27 patients after an initial evaluative interview with instructions that the placebo would have stimulant effects, and was not harmful or dangerous.

The effects were assessed by the patient for one hour. Reaction to the placebo test was as follows: 26% positive (n=7), 26% neutral (n=7) and 48% negative (n=13). Negative reactions were such symptoms as nausea, blurring of vision and other unpleasant effects. Unfortunately, here as well as in much of the literature, no distinction is made between unpleasant side reactions unrelated to the suggested effect and effects opposite to those suggested. For example, in this case, it may have been interesting to examine reports of drowsiness or relaxation attributed to the pill contrasted to those reporting stimulation as suggested. It is to Shapiro's credit, however, that he separated his neutral from negative reactors, while in the past the two groups were often lumped together. As it turns out, the distinction was meaningful in terms of characteristics of the group members. In general, it was found that the main distinction among groups was between reactors (positive and negative) and non-reactors.

Rickels and Downing (1967) report that in an earlier study placebo patients with psychopathology worsened initially when very sick, but improved slightly when initially less sick. In an unobtrusive measure, time taken to complete a mood scale, amphetamine instructed placebo subjects took significantly longer than sedative-instructed placebo subjects (Lyerly, et al., 1964). The authors attribute this effect to the subjects not trying to compensate for the "drug" effect on this task. Shipman, et al. (1974) reports exacerbation of symptoms while on placebo therapy, although no figures are given as to frequency of this response. Finally, Aletky and Carlin (1975) report a significant reverse placebo effect for male subjects on a dynameter task with the additional instructions that "subjects in good health and normal muscle tonus would be expected to show improved performance on the posttest." Thus, while reverse placebo effects appearently do occur, their frequency and dynamics are unclear.

A second body of literature bearing on the reverse placebo effect is that of the misattribution research. Many studies can be considered to have obtained significant reverse placebo effects (Storms & Nisbett, 1970; Ross, Rodin & Zimbardo, 1969; Nisbett & Schachter, 1966; Barefoot & Girodo, 1972). In these studies, subjects told to expect symptoms from a placebo source behaved less emotionally than the control group. Calvert-Boyanowsky and Leventhal (1975) present evidence that this effect is due to the preparation for arousal, although perceived arousal is not affected. More importantly, being given false expectations results in greater emotional behavior. When the true source of arousal or the neutral source is ambiguous (new drug), the researchers argued that manipulations of attribution would have the greatest chance of success.

This conclusion is in line with the theorizing of Valins and Nisbett (1972), who argue that a person receiving a "strong medication", who feels no effect, may then conclude his condition as deteriorated. Thus, "unfulfilled expectation of improved psychological state results in a worsened condition" (p. 270).

The question should be raised of why reverse placebo effects are so common in the misattribution literature and relatively uncommon in the rest of the literature. Several relevant distinctions should be borne in mind. The misattribution literature often contains contaminated control groups that may have increased emotional behavior, while the mere receipt of arousal information may lower emotional behavior in the experimental group. Also, the reverse placebo effects in the misattribution literature generally deal with behavior rather than feelings or reported arousal. The latter are

usually unaffected, but are the target for reverse placebo effects in most of the literature. Technically, insomnia effects such as in Storms and Nisbett (1970) may not be considered a reverse placebo effect since the pill was to affect arousal. However, practically, the desired effect was obtained in spite of no arousal change. One possibility to account for the apparent behavior/arousal self-report discrepancy is presented by Sternbach (1966), who argues that autonomic change may be more easily induced de novo by instruction than they are interfered with when the occur to some stimulus. The misattribution literature usually contains a natural source of arousal (shock, bedtime for insomniacs, the dentist) and finds that this arousal is relatively inflexible. The rest of the literature more nearly fits the former case.

One further puzzle must be considered before leaving this issue. None of the above theorizing clearly explains the difference between the results of Storms and Nisbett (1970) who obtained two reverse placebo effects, and the significant placebo effects of Kellogg and Baron (1975), and Steinmark and Borkovec (1974). All used insomniacs in their study. Since reverse placebo effects are hypothesized to involve a failure of expectations, is there any evidence of such a distinction among these studies? There is no direct evidence, but measures of belief in the placebo distinguish Storms and Nisbett from Kellogg and Baron. Storms and Nisbett found that belief in the placebo description was a significant factor in their results, and that arousal subjects believed the pills caused arousal significantly more than sedation subjects. Kellogg and Baron, on the other hand, found moderately low belief that their pills affected arousal symptoms. There is no data on the point, but it may be that the Storms and Nisbett subjects' beliefs reflect an initially higher expectation level, which led to relief in the case of the arousal subjects. The lower expectations of the Kellogg and Baron subjects may have led to a placebo effect, since expectations were realistic. The Steinmark and Borkovec study involved a therapy placebo rather than a pill, and this variable may be important for a number of reasons.

Side Effects

Side effects of a placebo can be defined as effects unrelated to the implicitly or explicitly suggested placebo effect which are due to the placebo. Thus, nausea in stimulant placebo subjects would be classified as a side effect if its occurrence was absent or significantly less in control subjects.

Side effects are commonly reported in the literature (Beecher, 1955; Pogge, 1963) but often are not strictly defined as above. The usual flaw in establishing the frequency of these effects is the lack of a non-placebo control group.

As perhaps would be expected, side effect literature usually concerns pills or other ingested substances rather than other forms of placebos. This is both because of the influence of the drug model in which side effects are common, and because the placebo side effect literature generally concerns a single placebo administration, while a placebo therapy operates over weeks.

Gruber (1956) reported negative side effects to a placebo drug, and found the side effects doubled when the placebo dosage was doubled. Clark (1969) in implying that his placebo was a narcotic found all but one of his subjects reported effects such as: slight headache, faint nausea, dizziness, depersonalization, confusion and euphoria. Beecher (1955) summarized his studies to report frequencies of definite symptoms to a placebo, but with subject and observer unaware that it was a placebo. Drowsiness was reported by 50% of the subjects, headache by 25%, and lesser percentages reported (in descending order of frequency) sensation of heaviness, fatigue, difficulty in concentrating, nausea, sleep, dry mouth and relaxation. Pogge (1963) is in general agreement with the ordering in his compilation of side effects.

Lower class patients are found to report significantly more side effects than other social classes (Rickels & Downing, 1967), a finding Rickels, et al. (1970) failed to replicate.

There is some evidence that incidence of side effects is negatively related to placebo improvement (Rickels & Downing, 1967). The finding that reverse placebo reactors had the most side effects and the neutral reactors the least also supports this view (Shapiro, et al., 1973).

A possible factor in side effects which may or may not play a significant role in their incidence is allergy. The so-called inert pill may be a myth, since allergic reactions may be engendered in susceptible individuals by virtually any food or chemical other than pure water (Mandell, 1973). Whether such allergic reactions are rare and therefore inconsequential is an empirical question, but certainly allergy cannot at this time be ruled out in the rare violent reaction to a placebo pill. Foods, even in minute amounts, can result in a wide range of symptoms including fatigue, stimulation, dizziness, flushing and headache (Rinkel,

Randolph & Zeller, 1951; Mandell, 1975; Mandell, 1973). A double-blind case study illustration of this is provided by Mandell and Rose (1968). While such severe allergic reactions are rare, it is probably that mild allergic reactions such as slight fatigue or headache are more common. Any attempt to assess the parameters of placebo side effects to ingested or injected substances must control for the possible contribution of allergy.

A Possible Placebo Reactor

The research on placebo reactors will not be extensively reviewed here. For discussions of this issue, see: Shapiro, 1971; Honigfeld, 1964a, 1964b; Rickels, 1968; Fisher, 1967. One perhaps neglected facet of this area concerns the possible role of the obese in placebo reactions. This possibility is derived from Schachter's (1971, 1964) line of research on the obese and internal and external cues. Schachter argued that the obese are stimulus bound (externally controlled), especially for high salience cues. For cues of low salience, the obese have been found to be less reactive than normals (Pliner, 1974a). Originally concerned only with eating behavior, this statement is now generalizable to many situations.

> With some confidence, we can say that the obese are stimuli-bound. There is little question that this is true of the eating behavior, and evidence is rapidly accumulating that eating is a special case of the more general case. (Schachter, 1971, p. 143)

How does this research relate to placebo reactions? The placebo situation can certainly be thought of as possessing salient external cues for relief of discomfort, since physicians or psychiatrists often administer the placebo with clear suggestions of effect within a setting emphasizing expertise and perhaps healing power. If placebo settings are indeed powerful external cues, presumably the obese should be more responsive to them. On the other hand, symptoms such as pain or anxiety are internal cues, and it may be that normals are more responsive to these cues.

Some evidence in the placebo literature seems to support this prediction. Rickels (1968) found extroverts, who presumably are responsive to social stimuli, may do better with placebos (also Honigfeld, 1964a). There is some evidence that extroverts withstand experimental pain better than introverts (Clark, 1969). Lasagna, et al. (1954) found placebo reactors to be "more dependent on outside stimulation than on their own mental processes" (p. 775).

Shapiro, et al. (1968) found positive placebo reactors tended to rely on outer stimuli, and may be field dependent.

Pliner (1973a) notes that the obese are more emotional than normals, another finding presumably congruent with obtaining prompt placebo relief. In a second study, Pliner (1973b) assessed the effect of external cues on cognitive activities of obese and normal subjects. Subjects were assigned a topic to think about, with or without accompanying slides depicting a scene from the topic (i.e., beach). This manipulation was intended to make the scene of high salience to half the subjects. As expected, a significant interaction was found between weight and cue salience for percentage of time spent thinking about the assigned topic. Of more interest was another analysis. Subjects also immersed their hand in ice water during the thinking trials, and latency to announcing pain threshold was timed. Again, a significant interaction was found between salience condition and weight for pain latency. The means fell in the predicted pattern for the obese subjects, although no planned comparisons were done. That is, the obese subjects had the greatest latency when slides were present, and lowest when no slides were presented. A control group was in the middle. The mean correlation for thinking time and pain latency was also significant, but low (.25). It was also found that the obese tended to think environmentally generated thoughts more than self-generated thoughts, while the normals tended to do the reverse.

In view of Clark's (1969) analysis of pain thresholds, it would have been of greater interest and pertinence to the hypothesis advanced here if pain tolerance levels had been assessed. Subjects could have kept their hands in cold water as long as possible, assuming no harm would result. This addition is necessary to distinguish simple demand effects differentially affecting the obese and normal subjects and actual increased tolerance to pain due to salient external cues.

If the hypothesis that the obese will tend to have greater placebo reactions in placebo settings is correct, then it may also followthat the obese will have the opposite reaction when placebo stimuli are low—for example, when taken alone at home or in an experiment with more salient stimuli present. In this case, a possibility for reverse placebo effects exists since external placebo cues are minimal or less salient than other stimuli.

Social Influence

There is a body of research that attempts to explain placebo responses in terms of social influence, demand characteristics or response bias (Pomeranz & Krasner, 1969; Clark, 1969; Sternbach, 1966; Morris & O'Neal, 1974). The change in reported symptoms is seen as being due to an implicit pact between researcher and client. Since the treatment is obviously supposed to help, the client may report that it did help, in spite of no actual change in the symptoms. The fact that most studies rely on self-report measures or assess subjective factors such as pain without incorporating physiological indices does not hinder this hypothesis. In the placebo situation, the demand is particularly clear, since subjects must know what the treatment is supposed to accomplish. Sternbach (1966) has argued that implicit demands play a role in placebo situations, but that "objective" change does occur because of these demands. Clark (1969) disagrees, arguing that verbal behavior is modified in pain perception, but actual suffering has not been altered. That his data support but do not prove his conclusion has been noted above.

A body of literature bearing on this issue concerns the possible role of social acquiescence in placebo results (Fisher, 1967; Pichot & Perse, 1968; McNair, Kahn, Droppelman & Fisher, 1968). Pichot and Perse perceive the placebo as "an acceptance of the therapeutic value of treatment, an acquiescence to the stimulus" (p. 52). Unfavorable effects would be produced by an attitude of rejection of the placebo, although no distinction is made between reverse placebo effects and side effects of the placebo (Pogge, 1963; Honigfeld, 1964a, 1964b). Two tests were used to assess social acquiescence, which only correlated moderately (.61), although both had face validity and were based on the tendency to agree with MMPI statements. In a study of the relationship of acquiescence to placebo response, 53 physicians were given four one-week drug supplies supposedly to determine the value of a new drug. Subjects were to indicate which weeks they received the placebo, and which weeks they received the active drug (Librium). Twenty-one doctors indicated they felt some effect during the placebo weeks, 22 felt no effect of drug or placebo, and only 10 correctly distinguished the two. It was found that the first two groups were significantly different on acquiescence on both scales. Unfortunately, acquiescence scores of the third group were not reported, although they were hypothesized to fall between the other two groups.

McNair, et al. (1968) compared the effectiveness of

placebo and drug treatment of 60 psychiatric clinic patients. Using a median split on acquiescence, no significant interaction was found for acquiescence and treatment after one week. However, after two weeks, significant cross-over interactions were found across nearly all indices of patient improvement, such that high acquiescers showed a more favorable outcome to placebo. Since the finding of placebo effect exceeding drug effect is rare in the literature (but not non-existent, Lehman & Knight, 1960), the researchers view it with caution. However, the lack of a difference between drug for low acquiescers and placebo for high acquiescers is probably reliable. But in the absence of a no-medication control, a possible correlation of social acquiescence with variables such as severity of illness could explain the results.

The relationship between social acquiescence measures and placebo response has thus been supported in two studies, although not universally supported (Shapiro, et al., 1973). If replicated consistently, what would be the implications for interpreting the placebo response? Although seeming to support the demand interpretation, social acquiescence cannot be equated with behavioral compliance (McNair, et al., 1968). In the study described above, it was found that acquiescers were no more likely to take medication, fill out all test items, or allow a follow-up interview than non-acquiescers. The researchers concluded that acquiescers are "thoughtless, non-discriminating individuals, rather than compliant conformers" (p. 71). In any case, it is not clearly demonstrated just what high scores on social acquiescence scales mean. Much previous research finding correlations with other personality measures suffer from inflated correlations due to being loaded on acquiescence (McNair, et al., 1968). Four possible interpretations remain for explaining the possible link between social acquiescence and placebo effects. First, social acquiescers could simply be unskilled and sloppy in reporting symptoms. Second, they could be complying with demands as they perceive them. Third, they may not be good at discriminating their internal states. A fourth possibility is that for some unknown reason, social acquiescers are particularly prone to developing genuine placebo reactions. No conclusive evidence has settled the issue. The first two differ primarily in intent, while only the third and fourth represent a possibility for genuine placebo-induced changes.

To counter the demand interpretation, many clinical anecdotes concerning objective changes accompanying placebo treatment exist (Wolf, 1959; Honigfeld, 1964a, 1964b; Shapiro, 1960), some of which are quite dramatic. Patients have developed rashes, became nauseous, increased gastric secretion

and engaged in other behaviors in response to placebo. Although some of these could be allergic reactions, it is unlikely all are. One unlucky man is even reported to have died after ingesting a placebo, an outcome researchers are understandably reluctant to replicate (Wolf, 1959). In a sense, these changes are responses to demands as Sternbach explicated, but they are not examples of simple distortion of self-report measures. But it is difficult to obtain objective measures of pain or anxiety and inconvenient to obtain them for insomnia, so self-reports have been relied upon. Frequently, results are not easily explainable in terms of demand. Storms and Nisbett (1970) obtained two significant results counter to the apparent demand of the experiment. Steinmark and Borkovec (1974) are fairly convincing in their demonstration of the efficacy of a placebo therapy for insomnia. Nash and Zimring (1969) argue that demand cannot account for their data since subjective changes and objective performances corresponded very well. It was found that placebo induced short term memory changes among high expectation subjects were consistent with experienced change to the placebo. Evans (1969) found that neither the experimenter's belief about whether the subject had ingested a drug or placebo nor the subject's own belief about what he had taken was related to the placebo response measures.

It would seem that demand cannot account for all placebo results, but neither can it be discounted as a factor in most studies. Tighter controls and incorporation of physiological measures and observer ratings would aid in establishing the parameters of the placebo phenomenon. Unobstrusive measures have also been unnecessarily neglected in this field.

A Model for Placebo Reactions

Theoretical frameworks for viewing the placebo effect have included so many variables that any model rapidly became unwieldy and vague. Demographic characteristics, personality variables, situational factors, physician characteristics, and diagnosis are examples of the investigated variables in the past. By theorizing at a more proximal level, two variables may be hypothesized to be crucial in determining the occurrence and intensity of the placebo reaction. These are the expectation and motivation of the recipient. It is hoped that these variables are useful in integrating diversified responses to many settings, symptoms and recipient populations.

Expectation

Expectation has appeared above, with its role clearly postulated in reference to the reverse placebo effect. Although some theorists have decreed a relationship between expectations and placebo response, the form of the relationship is fuzzy. That expectations play no important role in placebo effects has been argued by some (Honigfeld, 1964b) and others argue that it plays no role in therapy (Wilkins, 1973; Piper & Wogan, 1970). Others disagree (Shapiro, 1971; Nash & Zimring, 1969; Frank, 1973; Calvert-Boyanowsky & Leventhal, 1975; Valins & Nisbett, 1972; Steinmark & Borkovec, 1974), and claim it plays an important role in therapy outcome (MacReynolds, Barnes, Brooks & Rehagen, 1973; Goldstein & Shipman, 1961). Again, most research in this area contains serious methodological flaws, such as lack of manipulation checks.

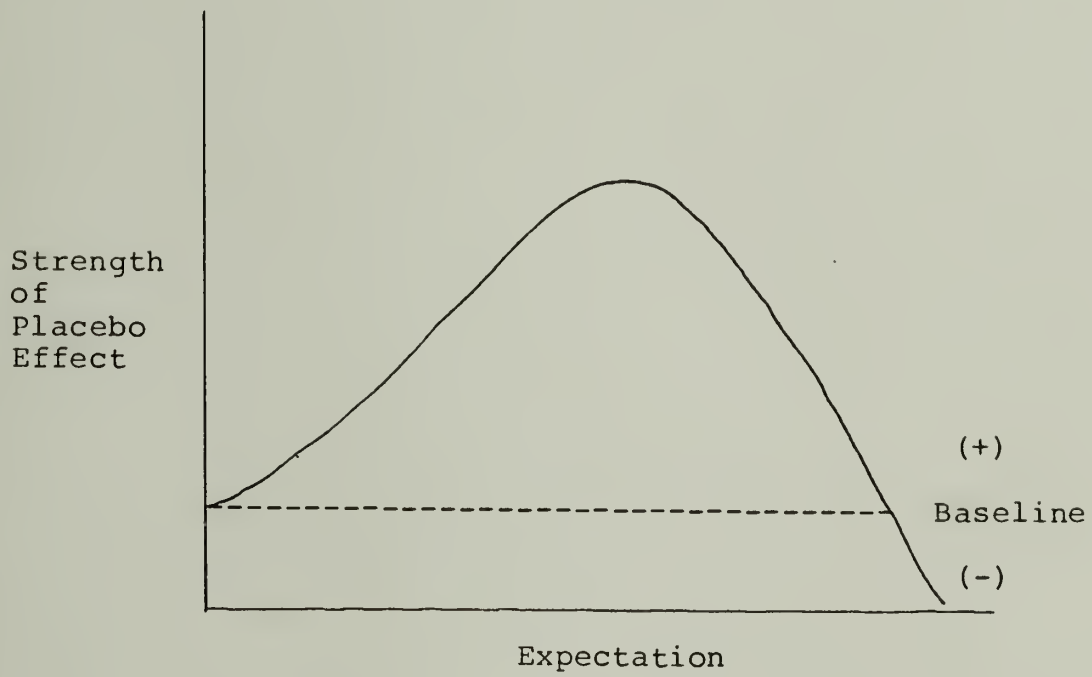
Wilkins presents strong evidence that expectancy state (as opposed to expectancy trait, which is relatively unmodifiable by experimental instructions) has little effect on psychotherapeutic gain when therapists are blind as to expectancy state. Although not blind to expectancy state, MacReynolds, et al. used a relatively complex pseudo-therapy rather than simple instructions as in the studies Wilkins reviewed, and found the placebo therapy was as effective in fear reduction as systematic desensitization. It could be that instructions do not affect expectancy greatly, since manipulation checks were often lacking. Expectancy trait was often found to correlate with therapeutic gain. Attribution of causality to expectancy based on correlational evidence is premature. However, the misattribution literature contains many manipulations of expectations with significant results, but with manipulation checks lacking. Steinmark and Borkovec (1974) found placebo results only when they were expected from instructions, and used an elaborate placebo technique to aid insomniacs.

The hypothesized relationship between expectations and placebo effects is illustrated in Figure 1. From a given symptomatic baseline, it is postulated that increasing expectations will lead to increasing placebo effects until the optimal level of expectation is reached, at which point maximal placebo effects will occur.

Expectations such as for symptom relief below this point are lower, and so is obtained relief. As expectations increase beyond the optimal point, they will be accompanied by less powerful effects, and very high or inappropriate expectations will lead to reverse placebo effects. The

FIGURE 1

The Relation of Expectation to Strength of Placebo Effect



appropriate expectation for optimal placebo effects operates within certain constraints. Obviously, some symptoms are not at all affected by placebos—i.e., a broken arm or atherosclerosis. Others are slightly affected and may call for more modest expectations than the most flexible ambiguous symptoms such as anxiety, depression or pain. The anxiety level of the client, social acquiescence score and other factors may also shift the optimal point right or left, as may the type of population studied (medical, psychotherapeutic or normal). Thus, the curve shown in the figure is really one of a family of curves affected by other variables such as those listed. But within a population, the curve should illustrate the effect of increasing and decreasing expectation levels.

The model must be empirically supported to be accepted, and such verification would require varying expectational levels with proper manipulation checks incorporated into the design. Several levels of expectation would be essential. Such studies are not available, but we can examine the existing literature to assess the plausibility of the model.

Honigfeld (1968, 1960b) sees persuasibility as a key factor rather than expectation, and believes expectation is not important in predicting treatment response. In regard to the first point, it is plausible that persuasibility and expectation will be related in a given setting. In terms of treatment outcome, Shapiro, et al. (1968) found a significant relation between placebo response and clinical treatment outcome. This was not replicated by Shapiro, et al. (1973), which the authors attribute to the use of psychotherapy rather than drug therapy as in the earlier study. Thus, a drug placebo stimulus may relate to drug therapy, and a verbal or "psychotherapeutic" placebo stimulus, such as free association in a quiet room, may be more appropriate to predict psychotherapeutic results. Certainly expectations may not be identical for a drug placebo and psychotherapy treatment.

Beecher (1968) cites evidence for set antedating surgery to expect relief leading to greater placebo relief. Pichot and Perse (1968) argue that a single expectational attitude may underly both placebo effect and response set. Wolf (1959) reviewed a study in which either doctors told bleeding ulcer patients a placebo treatment would work or nurses told them it might work. Positive results were at least three times as frequent in the first group. Rickels (1968) found that psychiatrists high on the F scale and extroversion did better with drugs, presumably due to enhancement of the placebo component of the drug response. Placebos were more effective for the acutely ill than the

chronically ill, perhaps due to less hope in the latter group. Placebos produced more improvement in an experimental set than a therapeutic set, perhaps due to higher expectations for the new. Those who expressed high confidence in the doctor were found to improve most with placebo treatment. Storms and Nisbett (1970) found experimental effects only when the subjects believed the pill description.

Experimental manipulations that may affect expectation are consistent with the model. Lowinger and Dobie (1969) found doubling of the placebo dose led to doubled rate of improvement, and Gruber (1956) obtained similar results for side effects. Evans (1975) reports that the effectiveness of the placebo in double-blind settings is a direct function of the strength of the active agent. Rickels, et al. (1970) provided some evidence for greater effectiveness for 4 placebo pills versus 1 pill per day. When the comparison was between 5 and 8 pills, no differential effectiveness was found, perhaps due to little perceived difference between the two dosages. Presumably, at some dosage point patients will become concerned with receiving a "dangerous" number of pills.

Nash and Zimring (1969) found expectations to be significantly correlated with both experienced change and short term memory change on a placebo drug. Friedman (1963) found patients with high improvement tended to have had high expectation levels significantly more often than those reporting little improvement. When expectations become unrealistic, less than optimal improvement may follow (Goldstein & Shipman, 1961).

The model also stipulates that factors other than expectation must be controlled within a population. Anxiety level, type and severity of pain and other variables will also effect the curve for a given individual. For example, as implied above, for high state anxiety a higher expectational level would be appropriate than for low state anxiety.

The effect of type and severity of psychopathology on the curve is unclear, since few studies directly bear on the issue. The two that do, however, lack measurements of expectational level. Fischer and Dlin (1956, in Kurland, 1960) gave placebo pills to 75 patients classified as psychotic, severe neurotic or mild neurotic. It was found that the mild neurotic group was most positive in response, followed by the psychotic and severe neurotic groups. Shipman, et al. (1974) found similar results in a study of placebo pill response among normals, hypernormals and neurotics under either normal or strong suggestion conditions. No main effect for personality type was obtained. While

the normals responded well to ordinary placebos, they responded less well to strong suggestion. The neurotics and hypernormals behaved in an opposite fashion. In both studies, it may be that the least pathological group was nearer the optimal expectation point. The addition of strong suggestion in the Shipman, et al. study may have pushed the normals over their optimal point, while raising the neurotics and hypernormals nearer that point.

Future research on the role of expectations should include manipulation checks and a wide range of expectational levels.

Motivational Variables

Motivational variables undoubtedly play a role in the placebo response. Social influence, demand characteristics, desire to improve, and social acquiescence may all enter into the response.

Many writers have noted social influence factors in the placebo situation as being important in determining the result of the placebo administration (Gelfand, et al., 1963; Pomeranz & Krasner, 1969; Goldstein & Shipman, 1961; Aletky & Carlin, 1975). Demand characteristics are one form of motivation, and although usually considered artifactual in the laboratory, may also operate in influencing behavior in real world settings. Pomeranz & Krasner found subjects receiving a placebo salve pulled harder than control subjects. Here the "medical" experimenter is perhaps similar to a real physician or psychiatrist, and may have a similar effect on overt behavior . Rosnow and Aiken (1973) have conceptualized such influence in terms of receptivity, motivation, and capability. The placebo may serve as a vehicle for conveying demand in such situations.

Several of the studies involving probable motivational manipulations contain serious methodological flaws (Buckalew, 1972; Campbell & Rosenbaum, 1967; Frank, 1974) such as failure to control for regression effects. In spite of this, these studies and others generally find results congruent with Lehman and Knight (1960) in that placebo effects are counter to fatigue effects (Pomeranz & Krasner, 1969; Aletky & Carlin, 1975). Future research should manipulate and assess motivational states in studying placebo effects.

At a more general level, motivation may be important in affecting all placebo reactions. If one has an intellectual

expectancy that a placebo will cause an effect, but is in no way motivated to achieve the effect, it seems reasonable to assume such an effect is less likely than for a highly motivated person. Motivation may often covary with expectation, but one may be motivated to improve, and still have a low expectancy for such improvement. The neurotic may believe only drugs can relieve his distress, and may not believe in psychotherapy's beneficial effects. A psychotherapeutic placebo may be ineffective in such a case. As in many theories incorporating motivation as a variable, it is assumed that an optimal, intermediate level of motivation is best for achievement of placebo effects, and that both too little and too much is detrimental.

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A P P E N D I X D

DEPENDENT MEASURES (SELF-REPORT, EXPECTATION, AND GUESS)

1. Self-report of symptom severity

Slight 1 2 3 4 5 6 7 Severe

2. Expectation

To what degree do you expect to react on this trial?

1	2	3	4	5	6	7
Certain I won't react			Uncertain			Certain I will react

3. Guess of test substance:

What do you think the solution is? _____
(If you don't know, please guess.)

How certain are you of this?

Not at all certain 1 2 3 4 5 6 7 Certain

APPENDIX E

CATEGORIZING SELF-REPORT SYMPTOMS

1. Cognitive-emotional

This category involves symptoms primarily thought of, or most likely to be, cognitive or emotional such as:

A. Intellectual effects—ability to concentrate
B. Moods
C. Memory
D. Mental fatigue or stimulation
E. "Psychiatric" states such as depression, anxiety, detached feelings, floating sensations.
F. Other

2. Mixed

This category is used for symptoms involving both psychological and physical factors in significant amounts or symptoms ambiguous as to whether they are physical or psychological.

A. Headaches
B. Aches or pains
C. Fatigue (not labeled mental or physical)
D. Sleepy, drowsy
E. Other

3. Somatic

This category involves symptoms primarily thought of or most likely to be somatic.

A. Flushing, chills
B. Heart rate increase
C. Nasal congestion
D. Muscular weakness
E. Physical fatigue
F. Cramps
G. Nausea
H. Other

A P P E N D I X F

SELF-REPORT SEVERITY SCORING

1. When subjects report old symptom, but severity number is less than or equal to previous level, give +1.

2. Average score when one judge says old and one says new.

3. When previous score of a symptom was corrected, use the raw score to determine the new level. For example, if on three occasions, a subject reports a headache at 7, 4 and 6, the severity scores would be 7, 1 and 2, respectively.

4. If a person notes improvement, give credit for the degree of improvement.

5. If symptom(s) goes away and then returns on a test, give full credit as if new.

6. If a subject just reports feeling better with no number, give 1.

APPENDIX G

SAMPLE MMPI CASE HISTORIES SUGGESTIVE OF ALLERGY

P. Hypo. M:27:S:24 +3 12386'7-(59) 7:6:9
+20 '93-4126(43) 6:1:18

Approximately six months before admission the patient suddenly began having upper abdominal "gas pains" which seemed to press against his heart. In addition to these attacks, which usually came at night, there was nausea, a hacking cough, numbness and tingling in his extremities, tinnitus, and a tired feeling which made him unable to work. Neither treatments of his own nor those suggested by a local physician relieved the symptoms. Although hard work apparently made the pain more severe, rest did not seem to help him in any way.

There were a number of episodic illnesses in his past history, including a tonsillectomy and an appendectomy. At one time he was hospitalized four months for tachycardia and associated nervousness.

The patient attended a country school until he was 16; he did fairly well, but his numerous illnesses prevented him from continuing his education, and from that time on he did farm work. He enjoyed track and baseball, apparently got along well with people, and was fairly adequate socially. He had always lived with his parents, who more or less told him what to do. Although he wanted to be an electrician or a mechanic, his family made it plain to him that they thought he should stay on the farm. His only spending money came from such work as he could do for his neighbors. He had had several girl friends and had had intercourse a number of times. His illness kept him from marrying.

When he was admitted to the hospital his mental content and general mental abilities appeared normal. He expressed a desire to get rid of his "gas pains" (which became better almost immediately on admission). There were no obvious disturbances of mentation. He was low normal in intelligence. His emotional tone was good. He was cheerful, friendly, cooperative, and easy to talk to, although he had poor insight into the possible psychological background of his problems. He got along very well, made friends, and entered into ward routine. It was felt that he might be better adjusted if he could in part break away from his family

ties and take some such job as filling station attendent, since he disliked farm work. At the time of discharge he was markedly improved, but of course he was still a very inadequate person.

P. Hypo. Schizoid F:23:S:58 +10 31'2648-(66) 6:5:14

The admission complaints for this young woman centered around headaches, pain in her side, insomnia, fatigue, dizziness, and anorexia. Two years before admission the patient had had periods when, she said, "I felt as if I were doped." These lasted for several hours and recurred several times a month. At the same time she became dissatisfied with her job in a grocery store; also, a brother, whom the family regarded as "the pet," was called into the navy. As time went on other physical symptoms were added to the original pattern. Her home medical doctor suspected hyperthyroid and prescribed medications which gave no appreciable relief. Much of the time during this period she stayed in bed. Finally she was admitted to the general medical clinic of the hospital where extensive studies were made for systemic diseases, with negative findings.

Never as robust as other children, the patient had avoided strenous activities and had suffered from "anemia." Her father was a tenant farmer and she had felt inferior because of the low social standing of the family in the community. Her father was frequently drunk. She made a "C" average in school and graduated from the eighth grade at 14. She did housework for five years, then clerked in a grocery store until the present illness appeared. She disliked the clerking job and felt unjustly treated by her employer. Described as always shy and retiring, she was dependent on others. Quiet entertainments such as reading and walking satisfied her. Although she often worked in the evening to earn extra money, she had no ambition for a higher level job than housework. She had never attempted to leave her home environment, although she had opportunities to do so.

Uppermost in the patient's mind were worry about her home condition and a shallow concern about her illness. She appeared to be only moderately depressed and was apathetic about future plans and ambitions. She remained convinced that she had an organic illness. Laconic in her answers during the examinations, she volunteered no additional information. Her appearance was neat and her manner pleasant. Physically she was inactive. During hospitalization she showed no marked improvement, although she did become a little more active. The complaints and the apathy seemed basically unchanged. Attempts were made to remove

her from the home environment but these having failed, she was discharged as unimproved.

P. Mixed	F:34:M:102	+1	32'1-9647(74)	3:3:10
P. Psychas.		+90	3'129-(53)	3:1:13

The patient's chief complaints were emotional instability, fatigability, insomnia, headaches, irritability, depression, and anorexia. These symptoms had been insidious in onset. About three years before admission she had had a "nervous breakdown" following a difficult pregnancy and delivery. Shoftly before this episode her husband had been inducted into the army. She had required repeated reassurance from her physician and had finally been sent to the hospital for psychiatric examination. When she realized the nature of the examination she became indignant and left without completing the study. The return of her husband from the service pleased her but no improvement followed. The fatigue, particularly, persisted.

She was described as moderately friendly and given to frequent discussion about other people's activities; her interests were chiefly in reading and handicrafts. She was orderly and excessively clean. She had always been thought of as high-strung and irritable. Ten years earlier she had engaged in frequent sexual relations with a man who later abandoned her. Depressed after this, she did not appear ever to have recovered from the experience. She claimed to love her present husband but sexual intercourse with him had been unpleasant and unsatisfactory.

Disturbed at being in a hospital, she was afraid that she might have to remain a long time. She presented a beautifully arranged history of her illness with only slight intervention and guidance by the interviewer. There were evidences of extreme nervousness but little insight into the psychological factors in her problem. She related incidents showing that she had always been a meticulous person. She was given electroshock therapy, which was followed for a while by untidiness, forgetfulness, and other evidences of organic deterioration. However, before her final discharge she improved, and while the basic pattern of symptoms remained, she was somewhat more cheerful. An effort was made to improve the sexual compatibility of the patient and her husband, but he did not cooperate and little progress was made. In contrast to the man with whom she had earlier had intimacies, her husband was ineffectual and indecisive. It became clear that she feared pregnancies but felt a conflict because during pregnancy she was relieved of sexual intercourse. The presence of a long-standing pattern of complaints and inadequacy, together with her

failure to develop much real insight, lowered the probability of complete recovery. However, at discharge, she had made positive improvement.

Ps. M-D., Depr.	M:42:M:17	+1	728436'19-(71)	5:7:19
		+14	'24783-(57)	4:2:21
Ps. M-D., Depr. Suicidal	M:42:M:9			
P. Mixed	M:42:M:52	+6	427'3819-(59)	4:5:22
		+19	'4873-(51)	5:5:21

This man was troubled by inability to concentrate or to sleep and a feeling that he could not continue to work. He dated this illness from ten years before when he had a number of somatic difficulties. Since then the symptoms had been irregularly present. Two months before admission it became unusually difficult for him to continue at his job. He said, "I feel like a machine on which I can't find the right button to push in order to make it get into action." Several mornings he returned home from his office and went to bed. At times he broke down and cried. He consulted a psychiatrist but discontinued treatment after a few interviews "because I felt much better and thought I could like this problem by myself."

When the patient was a junior in college he began to feel depressed and quit school for one year. During that time he was seclusive and avoided his friends. He took a job, however, and later returned to college with no further difficulty. During his boyhood he had always felt different from others, although the actual points of difference were unclear to him. Successful in his work, he was not affected when one of the men under him was advanced to a position superior to his, but later when he himself was promoted he exhibited tension and nervousness. Of a pleasant disposition, he was a fairly social person, yet he never formed deep or lasting friendships. He had five children and the family appeared to be a relatively happy one.

In the hospital the patient was oriented and apparently normal in sensorium and intellect. His discourse indicated self-condemnatory thoughts. He had insight about the emotional aspects of his illness, yet he did not understand how he could have developed the problems he felt he had. His adaption to the hospital routine was good and superficially he seemed normal. Somewhat casual psychotherapeutic efforts led to improvement. There was considerable evidence of dependency and some conflict in sexual matters. At the time of discharge he was nearly recovered

from the episode. He went home, got a good job, did fairly well for three months, and then suddenly regressed. He came back to the hospital after being found under his car in what appeared to be a suicidal attempt. After a short stay he again was apparently well and left, only to return in another three months with the same problem.