THE PLACEBO RESPONSE:

A STUDY OF THE PERSONALITY CORRELATES OF PLACEBO REACTORS

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PREFACE

I wish to acknowledge the help of my supervisor, Professor C.A. Gibb. In particular I appreciate his willingness to permit work on a topic only marginally related to his own area of greatest interest. Also, my thanks are due to Associate Professor P. Pentony, who assumed responsibility for my work in Professor Gibb's absence, and to Dr. N. Cox and Mr. Gavin Seagrim for their moral and practical support in attacking many problems.

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students at the Australian National University, who had the trust and temerity to place their faith in the name of the Department of Psychology, to the point of being willing to submit themselves as research material to aid in the study of an "unknown drug."

SYNOPSIS

A definition of placebo accepted in this study was that of "an inactive substance or preparation, formerly given to please or gratify a patient, now used in controlled studies to determine the efficacy of medicinal substances." The placebo effect was accepted as any effect attributable to a pill, potion or procedure, but not to its pharmacodynamic or specific properties. The placebo was distinguished from the placebo effect, the placebo being the agent which might or might not result in the effect.

Many questions about the placebo have become pressing. How does it work? On whom does it work? When does it work? While the use of the placebo is not new, the wide variability of its effects and the factors influencing this variability, have remained relatively unexplored areas. Most reports in the literature have consisted merely of the citing of such an effect, with little or no additional information being offered to account for the underlying psychological and physiological variables involved.

The opportunities opened by the placebo are unique, for it cannot possibly enter into any process by virtue of its chemical composition. The following are some

reasons why research in this area appears vitally necessary.

(1) Placebo reactors may change the slope of the dosage - to - response curve, and in consequence the sensitivity of the experiment.
(2) An effective durg may be wrongly discarded because data has been diluted by inclusion within the test group, a large number of placebo reactors.
(3) The optimal dosage of a standard drug may be underestimated if the placebo reactor group within the population is large and readily relieved.

The aims of the present study were to find if any consistent type of placebo reaction was elicited from a group of experimental subjects, and to attempt to study the relationship between particular personality variables and the tendency to react to the administration of placebo. A questionnaire was developed to measure these reactions. It was given to forty-five female subjects for four days, and then for another four days while these subjects received placebo, administered as an unnamed drug on which an experimental survey was being carried out. In addition, a control group of matched subjects filled in the questionnaire for eight days. The M.P.I., and T.M.A.S. were used as definitions of the personality traits of

anxiety, extraversion and neuroticism. A placebo reaction score was developed. This was the total frequency of response change shown by any one subject, when her pre-placebo responses were compared to her responses while receiving placebo.

It was found that a placebo effect had occurred in the experimental group of subjects. Not only was there a significant difference between the experimental and control groups as far as the total number of changes in response was concerned, but the two groups displayed different patterns of total frequency in response. After the introduction of placebo the experimental group showed a significant decrease in the number of symptoms reported (attributed to the fact that the majority of subjects who proferred an opinion as to the type of drug administered thought it a depressive.) However the control group exhibited a spontaneous recovery in response.

A correlation of ·35 was found between anxiety, as measured by the T.M.A.S., and the tendency to react to placebo. A correlation of -.30 was found between extraversion and the tendency to react to placebo. It was concluded that reaction to placebo in this study would seem to be an overt indication of manifest anxiety as defined by Taylor. In addition, Eysenck's description of the introverted neurotic, or dysthymic, as showing

symptoms of anxiety, would appear to clarify this result.

In addition it was found that high anxious subjects reported significantly more symptoms than low anxious subjects, before placebo, as well as after receiving placebo, and that these subjects also reported significantly more "toxic" symptoms in the two situations.

In so far as generalisations can be made from the present study, it was concluded that high anxious subjects would tend to react to placebo and that these subjects would also be dysthymics, as the correlation reported by Eysenck (1959) between the T.M.A.S. and extraversion was -.35.

It was recommended for more valid research procedures, where the efficacy of a pharmacological or physiological process was being investigated, that all subjects used in the experimental and control groups be matched on the personality variable of anxiety, and possibly introversion, and that a control measure of pre-test symptoms be taken if total symptom frequency is to be used as a measure.

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SECTION I

HISTORICAL BACKGROUND

The placebo has for centuries been used by physicians as medication on pragmatic grounds - that 'it helped patients.' Perhaps this is what motivated Sir William Osler to remark in 1905 that "the desire to take a medicine is one feature which distinguishes man, the animal, from his fellow creatures." Although the pharmacologic effect of a drug may have been deleterious or of little consequence to the organism, its effect could have been beneficial. Indeed, this is the history of medical treatment for the most part until relatively recently, since a great many medications of the past are now known to have been placebos.

The History of the word "placebo."

Pepper (1945) traces the history of the word, which is also listed in Webster's, 1940, and the Oxford, 1933, Dictionaries. As the first person singular of the future indicative of the Latin verb "to please," the word "placebo" literally means "I shall please."

Sir Walter Scott used it in the sense of a soothing sentiment. It was defined as "a commonplace

method of medicine" in the 1878 edition of Quincey's Lexicon, and in the Philadelphia Medical Dictionary published in 1808. Pepper points out that this definition may indicate the earliest stage of doubt concerning the efficacy of prescriptions of those days, and an approach to the frank admission of a quarter of a century later which appeared in the 1811 edition of Hooper's Medical Dictionary with the definition of the placebo as "an epithet given to any medicine adopted more to please than benefit the patient."

A more modern definition, implying an interesting methodological development, is that of the American Illustrated Medical Dictionary (Dorland, 1951) is "An inactive substance or preparation, formerly given to please or gratify a patient, now also used in controlled studies to determine the efficacy of medicinal substances."

Thus the placebo appears with a respectable connotation in medical terminology five hundred years after it was first used in other ways. Despite the frequent but perhaps unwitting prescription of placebos during the nineteenth and twentieth centuries, the word

placebo did not appear in the index of Wood's Therapeutics whose fourteen editions covered the period from 1875 to 1908. Kurland states (1960, p.115) "the resistance to and silence about this important therapeutic agent continues into the more recent history of the placebo."

THE PLACEBO EFFECT BEFORE 1900.

There are many indications that physicians and others, even from earliest times, were cognizant of "placebo-like" phenomena, although this was not referred to as the placebo effect, nor was it exhaustively studied or extensively written about.

Placebos have been used to alleviate human suffering since the beginnings of medicine, but not usually knowingly. Each medical era has brought forward chemical agents, efficacious at the time, but later found to lack the pertinent pharmacodynamic property. Countless herbs and potions fill the pages of text-books as prevailing fashions have changed with each generation, their placebo action deriving in part from the faith and enthusiasm of earnest physicians. Many such agents have died out without difficulty. When, from time to time, various

ones of them have been exposed as chemically useless, new equally intrinsically inert nostrums have taken their places, each enjoying its day of clinical effectiveness. Modell (1955) writes that the placebo effect ".... is the only single action which all drugs have in common and in some instances it is the only useful action which the medication can exert."

The history of medical treatment is at times incredible. Even in all the pages of the work of Hippocrates, no treatments of specific value may be found. Four of the most famous medications that were used by physicians up to the sixteenth, and at times during the eighteenth centuries were: the fabled unicorn's horn to detect and protect against poisons in wines, bezoar stones as antidotes for poisons of all types, theriac as a universal antidote, and powdered Egyptian mummy to heal wounds and as an almost universal remedy.

Acute observers of their time, such as Montaigne in the sixteenth century, observed that doctors in general, were a danger to their patients. Earlier, in the twelfth century, Maimonides implied this in his statement, "I call him a perfect physician who judges it better to abstain from treatment rather than prescribe one which might perturb the course of the malady." (quoted Shapiro, 1960

p.112). Moliere's satires in the seventeenth century on the medicine of his time are well known. As late as the seventeenth century, a contemporary of Moliere, Robert Boyle, the father of modern chemistry, after expunging many questionable remedies from the revised pharmacopoeia, included the sole of an old shoe "worn by some man that walked much" which was to be ground into a powder and taken for stomach ache. Oliver Wendell Holmes said as recently as 1860, that nearly all the drugs then in use should be thrown "..... into the sea where it would be better for mankind and all the worse for the fishes." (quoted Shapiro, 1960, P.112.) Despite this, sick patients continued to submit to purging, cutting, cupping, blistering, bleeding, freezing, heating, sweating and shocking.

To-day we know that the effectiveness of these procedures and medications was due to the placebo effect, although little is known about how the placebo is effective.

Among the powerful circumstances which aid the placebo in alleviating symptoms and curing disease is the inherent, recuperative power of the human organism, the tendency for diseases to be self-limited. As long ago as 1800, Gall was asking himself, "What is nature's share and what is medicine's in the healing of disease." Before his time, the dictates of authority had determined pretty well what treatments would be used and the weight of authority was

considered adequate as evidence for the efficacy of a particular agent or procedure. Sixty-three years after Gall, bleeding was still the most popular treatment for pneumonia when Biclard, in one of the first well-controlled therapeutic experiments, proved that bleeding had no specific value. Nevertheless, forty years later, and despite his advice in 1903 to the young practitioner to "bear in mind that patients are more often damaged than helped by the promiscuous drugging which is still only too prevalent" he recommended for the treatment of pneumonia "Veratrum viride, Paquelin cautery, hot poultices, cold baths, Dover's powder, strychnine -- and bleeding."

THE PLACEBO EFFECT FROM 1900 TO 1945.

Very few articles were written on the topic during this period, and the word was not used in its present meaning until the 1930's. Cabot in 1906 discussed the ethics of the "Nostrum Evil" referring to the placebo as quackery. In the same year Fontus (1906) in his text on pharmacy and prescription writing, briefly mentioned the positive indications for the use of placebos.

It was not until 1908 that Rivers produced "The Influence of Alcohol and other Drugs on Fatigue," and in this he used inert material, not referred to as a placebo, as a control. The latter was designed to taste and appear

indistinguishable from the experimental drug. As the subjects and experimenter had no knowledge of which substances the subjects were receiving, it was one of the earliest anticipations of the double blind procedure. It represented a very early understanding of some of the powerful effects of the placebo in experimentation.

Ayman (1930) discussed the concept of the placebo without mentioning the word as such, in a paper in which he evaluated the therapeutic results in thirty-five papers on essential hypertension. He found that in every paper complete or partial symptomatic relief was described. Up to 85 percent reduction in blood pressure was reported - with mistletoe, diathermy, watermelon extract and Nauheim baths as some of the therapeutic agents : Ayman himself treated forty patients with drops of diluted H Cl t.i.d. and 82 percent showed definite improvement. He concluded that the common element was the enthusiastic giving or doing of something to the patient.

But it was not until 1938 that Houston, in an article entitled "The Doctor himself as a Therapeutic Agent," actually used the word placebo extensively and discussed some of the factors involved in the placebo effect.

However, during this period, not only was the literature on the placebo surprisingly meagre, any principles that were elucidated were not absorbed into the mainstream of

medical research and practice.

It was not until 1945 that interest was awakened in the topic, and in 1946 we find DuBois stating that "....the study of the placebo is the most important step to be taken in scientific therapy." He continued, "....although placebos are scarcely mentioned in the literature, they are administered more than any other group of drugs .... that although few doctors admit that they give placebos, there is a placebo ingredient in practically every prescription .... that the placebo is a potent agent and its actions can resemble almost any drug." (quoted Shapiro, 1960, p.121.)

Because of the added amount of interest from 1945, it will be necessary at this point to investigate the problem in greater detail.

The turning point came with the advent of the 1945 Cornell Conferences on Therapy, at which the use of placebos in therapy was discussed. From this point the results achieved by studies of placebo acquired a limited aura of respectability. In addition, a necessary attitude of sophistication in approach began to develop. The "placebo reaction" per se, was recognised and demarcated, and an accepted definition arose, that the placebo reaction "is the physiological and psychological reaction to the

administration and acceptance of the placebo." (Fischer and Dlin, 1956, p.510).

At the Cornell Conference, DuBois suggested that placebo be divided into three categories. The first was the pure placebo, such as the bread pill or lactose tablet, which has no possible intrinsic action. The second was the impure placebo i.e., adulterated with an active ingredient which might have some pharmacologic action, such as tincture of gentian or a very small dose of nux vomica, but which has no relevant effect upon a patient. The third is "the universal pleasing element which accompanies every prescription." (DuBois, 1946, p.1719.)

The Conference supplied much additional material, almost in the nature of revelations. For example, the statement by Grace could perhaps be classified as a scientific confession.

> "It is well known that the response to a particular pharmacologic agent in a group of patients is not invariably the same or even predictable. When we learn that a certain agent proved effective in, say, 35 percent of the patients, we accept the result and let it go at that. This is one way of evaluating a therapeutic agent. There are other questions which need to be raised and answered. I refer to the matter of determining the factors in any particular individual which alter the responses to the drug in question from time to time. It helps to understand why an agent may fail to work at one time or produce more effect than anticipated at another." (Gold, 1954, p.722.)

From the more clinical standpoint, Deithelm raised some important issues, and for the first time the concept of suggestibility was openly introduced as a possible variable.

> "We have to consider the patient, the drug and the physician in evaluating the effect of a drug. In evaluating the patient we have made very little progress. We know little about the meaning of suggestibility. It refers to the ability of a person to react in a positive way to suggestions. The concept is no doubt very valuable, but little progress has been made in understanding what factors permit the person to be more suggestible from the truly psychobiologic point of view ..." and again, "No doubt the factor of belief is very important in the reaction to a drug, but again, when we try to understand from a medical point of view what belief means, we are considerably handicapped. The older formulation is that the person reacts to suggestion because what is suggested to him becomes a reality within that person; he believes in it, and, therefore, the expected result will take place. This is obviously possible only within a very limited range, but within this range it is definitely a fact." (Diethelm, 1946, p.1721.)

However, possibly the most significant figure at that time was Gold, who not only was a major influence in bringing the attention of his colleagues to the importance of the placebo, but was responsible for the formulation of the term "blind-test" which later became the "double-blind" procedure of control. Probably the most important single statement of the conference was his pronouncement,

> ".... I have reference to a comparison of one compound with another, an attempt to determine, for example, by how much one compound is more potent than another in relation to a particular effect. The moods and attitudes of the patients used in such comparisons are very important and influence the results, but it is possible so to design the evaluation that whatever influence the emotional state of the patients may exert is cancelled out by having it distributed between the two compounds used in the comparison. The two compounds may involve an allegedly potent agent and a blank of such physical properties as to render a distinction between the two impossible except through some pharmacologic potency which may exist. On the other hand the two compounds may both be potent, and we test them to determine a difference in potency. In this type of evaluation of a new drug there are two indispensable elements: one is the notion of a comparison of one thing with another, the other is the factor of the double-blind procedure .... The failure to use the double-blind test and the placebo in the attempt to evaluate a new drug is responsible for a large proportion of erroneous conclusions in clinical testings." (Gold, 1954, p.722.)

Gold went on to point out that the whole history of therapeutics, especially that having to do with the action of drugs on subjective symptoms, demonstrates that the verdict of one study is frequently reversed by another unless one takes measures to rule out the psychic effect of a medication on the patient and the unconscious bias of the doctor. He considered the double-blind test ensured this.

It was at this same Conference that Wolff reported the relations of the placebo effect to his experiments on pain thresholds, in what he called "suggestible" and "non-suggestible" subjects. The pain threshold was measured by exposing an area of skin to heat from a 1,000 watt lamp. It was expressed as that amount of heat in gram calories per second per square centimetre which just elicited a sensation of pain at the end of a three second exposure. This threshold was approximately uniform from individual to individual. With this method, it was found that 0·3 gm. of acetylsalicylic acid predictably raised the pain threshold approximately 35 - 40 percent above its control level before the administration of the analgesic agent. It was also observed however, that it was possible to raise the pain threshold by administering a sucrose tablet to an individual who believed that he was receiving a tablet of acetylsalicylic acid. It had been demonstrated elsewhere that the pain threshold elevating effect of an agent such as acetylsalicylic acid is appreciable and reproducible. However these experiments showed that a similar threshold-raising effect could be obtained with a placebo "if the subject can be convinced by suggestion that he has received an agent which will raise the pain threshold." (Wolff, 1946, p.1720.)

From this point, the effects produced when presumably inert substances (e.g. lactose and saline) were given to normal and diseased individuals became appreciated by many. An attempt was made to describe the lesser known aspects of the "pharmacology" of the placebo, by depicting the ways in which the clinical use of inert substances may lead to effects which are usually considered to be the exclusive property of active agents.

After work conducted in 1950, Wolf stated,

> "It is important to realise that placebo effects are not imaginary. Neither are they necessarily suggestive in the usual sense of the word. For example, certain workers have induced changes in circulating eosinophiles[1], either during the discussion of meaningful topics or following the administration of placebos. Eosenophilia, a phenomenon of which the patient may have no knowledge whatever, could obviously not be achieved by suggestion. Perhaps a person could think himself into a disturbance such as sweating or tachycardia, or even hives on the skin, but hardly eosinophilia." (Wolf, 1959, p.694.)

When Cleghorn et al., (1950) were able significantly to activate adrenocortical activity by the hypodermic injection of sterile saline, and Rainzler et al., (1953) were able to effect a statistically significant reduction in the concentration of serum lipoproteins by the administration of placebos, Wolf claimed that all of these findings indicated that the responsible mechanisms were

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1. Eosinophile: a Leucocyte or other granulocyte with cytoplasmic inclusions. An abnormal increase in the number of eosinophiles in the blood is characteristic of allergic states and various parasitic infections.

connected with circuits in the cerebral cortex. "Thus for placebos a variety of modes of action become possible including suggestion, conditioning, and other as yet obscure mechanisms." (Wolf, 1959, p.694.) Gliedman et al, (1957) made the special point that placebo effect might be reinforced in the presence of a state of central excitation induced through conditioning.

However, it was Lasagna in 1958 who made the following important points, which had great relevance to pharmacology and its experimental methods. One of the basic indices of pharmacologic activity is the time-effect relationship, for when an active drug is given to patients, a maximum effect is typically achieved at a certain point in time. It was not widely appreciated that placebos can also show this behaviour.

A second type of basic study is the delineation of the effect of repeated doses of a drug. This was often considered to be a reflection of increasing concentration of drug in the blood or body. But as Lasagna brought to notice, it is not greatly appreciated that placebos can also show a "build-up" in effect, and that there may be a "carry-over" after cessation of placebo therapy.

Another general characteristic of drugs is the inverse relationship of their efficacy to the severity of a given complaint. The same relationship for placebos

was apparent in data reported by Lasagna. In a study of the efficacy of morphine and injected saline on postoperative pain, Lasagna (1954), found an inverse relationship existed between the number of doses of medication required post-operatively and the efficacy of morphine or placebo. That is, the effectiveness of both morphine and placebo diminished relative to an increasing number of doses for relief of postoperative pain. (see Table II, p.37.)

It came to be accepted that to understand better the pharmacodynamic effects of drugs, it was necessary to explore the role that such other determinants as hospital, social class, staff and other patients, play in the dynamics of the test subject.

The recognition that mood-changing drugs acted in complex ways arose out of findings that were contrary to classic text-book descriptions of drug action. The analgesic effect of morphine was found to be improved by an informal, friendly attitude toward the subjects. (Kornetsky, 1957.) Cocaine and hasheesh did not always produce euphoria (Lindemann, 1934.) Amphetamine might be pleasant to one person and unpleasant to another (Lasagna, 1955.) A great distinction was made between the primary, physiological drug action, and the secondary or subjective response to the drug. These investigators brought awareness into some of the non-pharmacological problems involved in drug experimentation with man.

To study the placebo's implications for theory and research, we need to survey work conducted on it, and its

effects, in more specific areas. The need for this is clearly seen in Beecher's summary of the many purposes and uses of placebos.

> ".... as a psychological instrument in the therapy of certain ailments arising out of mental illness, as a resource of the harassed doctor in dealing with the neurotic patient to determine the true effect of drugs apart from suggestion in experimental work, as a device for the elimination of bias not only on the part of the patient, but also, when used as an unknown, of the observer, and finally, as a tool of importance in the study of the mechanism of drug action." (Beecher, 1955, p.1602.)

THE CLINICAL APPLICATION OF PLACEBOS

As early as 1938, one hundred million dollars was spent by the American public on vitamin preparations. This meant that approximately 10 percent of the nation's medical expenses was spent on vitamins, which are so often prescribed both knowingly and unknowingly for their placebo effect. (Journal of the Amer. Med. Ass'n., Council on Food and Nutrition, Vol.1, 1959, p.41.) Dunlap, Henderson and Inch (1952) analysed over 17,000 prescriptions of physicians from representative areas in Great Britain for a one month period. Approximately one third were considered to be in the placebo category. The British Medical Journal (Vol.1, 1952, p.149) editorialised that, ".... a bottle of medicine is given as a placebo in about 40 percent of the patients seen in general practice."

Attitudes toward the use of placebos in treatment therefore require some comment at this time for several reasons. There is little unanimity of opinion about the indications for their use, though the subject has been discussed extensively. Many would agree that all or some of the following were indications for the administration of placebos. (1) They can be used for patients with incurable diseases (Pepper, 1945, Editorial, Lancet, 2, 1954.) (2) A placebo can be substituted and dissipate a confusing clinical picture of a patient taking a conglomeration of drugs (Modell, 1955, Leslie, 1954, Abramwitz, 1948.) (3) It can be used for elderly or chronic patients who have become used to placebos; (Editorial, Lancet, 2, 1954) (4) for post-operative patients weaned away from opiates to prevent habituation; (Editorial, Journal Amer. Med. Ass'n, 159, 1955) (5) for psychoneurotic patients who need a material sign to establish confidence so that they may benefit from the psychotherapy that follows; (Carter, 1953) and (6) in patients with strong dependency needs for emotional security the placebo may be an added emotional link with the physician, (Editorial, Journal Amer. Med. Ass'n. 159, 1955.)

Its intelligent use can be of great help. "It is not whether the physician should or should not use placebos, but how he should best utilize this omnipresent effect. His need for justification for exploiting placebo action

is obviated, since he inevitably applied it whenever treating a patient, whether he seeks to do so or not." (Shapiro, 1960, p.202.)

However, like any other clinical method, there is much disagreement and debate about different definitions of placebo, used in a therapeutic context, about what constitutes the placebo effect, and about which therapies are effective independent of the therapeutic effect.

Some limit the definition of the placebo, as used clinically, to non-active (inert) medication, while others include active (non-specific) medication. Some limit the definition to medication (active or non-active) but only when it is given by a physician with full knowledge that a placebo is being prescribed, while others include medication which is prescribed without the physician's knowledge that it is actually inactive, non-specific and acting like a placebo. So, in this particular clinical context, the word placebo might best be defined as any therapeutic procedure (or that component of any therapeutic procedure) which is given to have an effect on or does have an effect on a symptom, syndrome or disease, but which is objectively without specific activity for the condition being treated. Some view any discussion of whether to use placebos as being only an academic question, since all therapeutic procedures can act as a placebo and

since all placebo effect is in part a consequence of almost all medical procedures. This would include, therefore, all medical procedures no matter how specific.

It is therefore acknowledged that the practice of prescribing placebos (knowingly and unknowingly) is inevitable at the present time, and is determined by the seeking of a level of use and disuse based on the ebb and flow of all the factors involved.

However the work of Wolf and his collaborators (1950) has stimulated more sophisticated and precise interest in the subject. They performed interesting anecdotal experiments on the patient "Tom", who had a gastric fistula. It was possible to demonstrate by direct observation that the effect of some drugs on the gastric function were directly dependent on "Tom's" emotional state, and that placebos could reverse the pharmacologic action of drugs and cause end organ changes.

In another paper, Wolf and Pinsky (1954) showed how placebos could cause extensive "toxic" reactions (examples of minor toxic side effects are sleeplessness, anorexia, nausea, drowsiness, vertigo, headaches, depression and palpitations) and they experimentally explored other aspects of placebo. They reported observations on thirty-one out-patients who acted as their own controls. They were anxious, tense patients, some of whom had

psychosomatic complications, such as peptic ulcer and migraine. The results with mephenesin tablets and an inert placebo showed that in either case 20 - 30 percent were better, 50 - 70 percent unchanged, and 10 - 20 percent worse. More surprising was the fact that major side-reactions such as light-headedness, drowsiness and anorexia, occurred frequently with both mephenesin and placebo, and in three cases there were major complications from those on placebo.

In 1955 Beecher summarised fifteen studies, which pertained to placebo effects in a total of 1,082 patients, suffering from such varied complaints as post-operative pain, headache, anxiety and tension, cough, and using such varied placebo substances as lactose, saline and bicarbonate. He concluded, "The constancy of the placebo effect (35·2 $\pm$ 2·2%) as indicated by the small standard error of the mean in a fairly wide variety of conditions, including pain, nausea and mood change, suggests that a fundamental mechanism in common is operating in these several cases, one that surely deserves further study." (Beecher, 1955, p.1605.)

From this Beecher claimed,

> "if against all of the evidence to the contrary, one were to hold the view that the placebo is a feeble or useless therapeutic agent, then the placebo should

> appear most effective when the test condition is mild and less effective when pitted against severe conditions. There are two kinds of evidence, subjective and objective referred to, that just the opposite is the case, placebos are most effective when the stress (anxiety or pain, for example), is greatest." (Ibid).

On the whole, although much of the data has anecdotal trends, it might be said that the response to placebo in the clinical situation is a very real phenomenon, although slavish devotion to the principle of requiring manifest causes for observed effects tends to cloak it with an atmosphere of mysticism.

THE USE OF PLACEBOS IN EXPERIMENTAL AND CLINICAL PHARMACOLOGY

Pharmacology may be defined as the science that studies the interactions between living organisms and chemical substances that have been introduced into those organisms. Whether it is the interaction itself that is studied, or whether the interaction is used in a bio-assay to evaluate the potency of potential or actual therapeutic agents, the requirements of a valid pharmacological experiment are the same.

A fundamental criterion of a valid experiment is that the phenomenon observed is the result of the experimental procedure, not of extraneous factors. In an experiment that involves the use of drugs this principle demands that the results obtained can be ascribed to the

effect of the drug and not to those of other factors in the environment. The response of a living tissue or organism that occurs in the absence of the active drug but under environmental conditions otherwise identical to those under which the drug produces a response, was known as a "blank" or "control" reaction or response, but the phenomenon is now recognised and consciously used as placebo. Under the most nearly ideal conditions, the magnitude of the placebo control reaction is zero. When the control reaction is not zero, one is forced to conclude that some variable other than the one being studied has altered the response.

Part of the design of a valid pharmacological experiment involves the choice of criteria of drug effect which are appropriate to the actions of the drug and which can be measured accurately and objectively. For example, although many drugs that lower high blood pressure in patients do so by virtue of a sedative effect, the experimental evaluation of the effectiveness of a possible antihypertensive drug must be made on the basis of its ability to lower blood pressure in experimental animals and not on its ability to cause sedation. Similarly, in testing a new agent for its value in the treatment of peptic ulcer, the investigator must distinguish between the effects of a drug in causing diminution in the size of the "ulcer"

seen on the x-ray film and the effects of the drug in diminishing gastric motility or gastric acidity, which may or may not lead to the healing of the ulcer.

The more selective a drug is in its actions the less likely it will be that other effects than those under study will obscure the desired responses in the intact organism. The broader the spectrum of action of the drug the more difficult it becomes to evaluate the type and magnitude of a single drug effect.

The design of an experiment in clinical pharmacology requires the same or even greater care than the design of an experiment conducted in the experimental laboratory. Provisions must be made for testing a new drug over a wide range of doses. But above all, account must be taken of the occurrence and magnitude of placebo reactions.

The non-placebo effects of a medication or of a procedure could be designated as its "inherent" effects, as opposed to the placebo effect. The distinction is abstract. In concrete reality there is probably always a combination of placebo effects and inherent effects. That is to say, a fully adequate pharmacological description of a drug should in the light of present knowledge, include a characterisation of the patient's attitudes which could determine differences in its effects. Because of this it has become more apparent to researchers

that to evaluate the inherent effects of a drug requires appropriate placebo controls.

It is clear that as a first step in design and in order for a therapeutic experiment to produce results which can be satisfactorily evaluated, it is necessary to know that the observed changes would not have taken place spontaneously. Again and again attempts to define the natural history of a disease, allowing for comparison of results of an untreated group with a series treated with a certain therapeutic agent, have failed to bear fruit in one disease after another.

At an early stage Pinel had suggested that the therapeutic efficacy of drugs could be tested by treating patients one year and not the next, but his data did not hold up because the severity of disease, especially infectious diseases, varies greatly from year to year. It was failure to recognise this fact that led to the conviction in the minds of many medical leaders in the late 1940's that chlortatracycline (Aureomycin) was effective in the treatment of atypical pneumonia. It was not until four years later (in 1953) and after many hundreds of pounds of Aureomycin had been used in the

treatment of atypical pneumonia that Walker published his controlled study of 212 cases in which Aureomycin was found to be no more effective than a placebo.

Haight (1954) applied the placebo control to his studies in the antibiotic field. In an investigation of the comparative effects of penicillin, erythromycin and placebo on the duration of illness in scarlet fever he found that those patients treated with penicillin and erythromycin recovered in less than half the time of those treated with placebo.

On the other hand, Grossman and Masserman found, in studying the analgesic and antirheumatic effects of Aspirin (acetylsalicylic acid) acetophenetidin (Phenacetin, p-acetphenetidin) and other agents, using a blind placebo technique, that the placebo was usually just as effective as the agent. They also observed nearly the same percentage of untoward reactions from the placebos as from the agents.

When izoniazid was first tried in tuberculosis, patients were photographed dancing in the hospital corridors. Since the drug could not have cured the

disease in this length of time, it was concluded that it was exerting a euphorogenic effect. Patients are no longer dancing and it is now clear that izoniazid does not induce euphoria. The early patients who received the drug were euphoric without a doubt, but the euphoria was not due to the pharmacodynamic properties of the drug. It was probably due to the fact that the physicians of these patients in the tuberculosis hospitals had just been suddenly converted from jailers to therapists, and it was their renewed hope and faith and pleasure in this event that influenced the patients and produced euphoria.

In this vein, in 1955 Shapiro noticed that in a study he was conducting on the value of hypotensive agents, the initial phase of the study was characterised by a positive attitude on the part of the investigator. During this period he was enthusiastic about the drug and its therapeutic potential, had great personal incentive toward the project, and maintained a warm and giving relationship with his patients.

> "After an interim period, during which certain events in the laboratory and the investigator's personal life (coupled with a preliminary analysis of the data indicating no striking effects of the drug) led to a dampening of the

> investigator's enthusiasm, the study entered a phase characterised by a negative attitude. At this time the doctor-patient relationship became stereotyped and impersonal." (Shapiro, 1955, p.297.)

The positive or "enthusiastic" attitude coincided with a period of lower blood pressures, while the negative or "nonenthusiastic" attitude was reflected in higher levels.

In 1956 Feldman followed up experimentally Shapiro's observations, in a particularly revealing study. Patients were catalogued according to how well they had done on individual tranquillizing drugs. In addition, an estimate was made of the degree of enthusiasm that the doctor had for the agent he was using. The correlation showed that those patients who had done the best were in the group treated by the doctors who liked the drug the best. Those who did poorly were patients of the therapeutic nihilists.

Gliedman et al., (1957) reported two groups of patients with bleeding ulcers treated with placebo. One group was told by the doctor that a new medicine would be given them which would undoubtedly produce relief. The other group was told by nurses that an experimental medicine would be administered, the effects of which were more or less unknown. In both instances, the same agent was employed, namely, the placebo. In the first group, 70 percent of the patients had excellent results, which in

the second group only 25 percent showed a favourable response.

From such studies it became obvious that in every branch of experimental therapeutics, including drug therapy and psychotherapy, researchers and evaluators had to take into consideration the accidental introduction of the really important therapeutic principle and of wrongly attributing the good results to the factor which the experimenter had in mind. Particularly in pharmacology, the misconceptions which resulted from inadequate experimental procedures, especially those ignoring or mishandling the placebo effect, spread rapidly and held sway for a long time.

Studies such as these caused Lasagna (1958) to point out that first of all, uncontrolled studies that claimed a new or old drug to have shown unequivocal therapeutic benefit, merely because of "peak effects" of "cumulative effects," or persistent benefit after cessation of treatment, should be interpreted with considerable caution. A placebo effect was obviously not an "all-or-none" phenomenon.

Secondly, the time-effect relationships of placebo phenomena might be extremely important in deciding upon

the times when data were to be collected in controlled trials. It was conceivable, for example, "that in a certain situation the effects of suggestion are rapidly obtained, but also wear off fairly rapidly. In another situation the effects may require longer to wear off." (Lasagna, 1958, p.536.)

In addition, a failure to collect data at points other than the placebo "peak" might give a misleading notion about the efficacy of an active drug being eveluated against placebo.

But it was probably the recent advent of the tranquilisers which pin-pointed the problems of assessment most acutely. The tranquilisers are the fastest growing drugs in history, and it was estimated that in the United States in 1957 they moved to second place in drug sales. They brought to general notice the obvious facts that the experimental biochemistry, physiology and pharmacology of the future would more and more concern man, and in such studies, answers must be sought to questions that involved man's subjective responses. For success in this area it must be recognised that the needs of this kind of investigation differ from those dealing with objective responses. Thus, with the advent of tranquilisers and the recognition of the importance of individual differences in reaction to drugs (Levin, 1959, Beecher, 1955) a

greater awareness was born of the importance of the design of therapeutic trials.

The growing understanding of the measurable effects which might follow administration of an agent but were not attributable to its pharmacodynamic properties, eventually turned the attention of workers in the area to the obvious fact that a large number of patients had little ability "to discriminate between the effects of active drugs and inert substances." (DeMaar et al., 1955, p.112.) Such persons were termed "placebo reactors" in contrast to those who were able to discriminate, if that were the mechanism involved, and were called "placebo non-reactors." The concept of the placebo reactor was a useful one, and carried enquiry a stage further.

THE PLACEBO REACTOR

Because each study encountered has been a major contribution to knowledge, and a major cause of controversy is in this field, it is proposed to deal with each in detail.

1. The Initial Study of Jellinek (1946.)

In 1946, under the somewhat unassuming and obscure title of "Clinical Tests on Comparative Effectiveness of Analgesic Drugs," Jellinek became the first to report and publish in detail, work on the placebo reactor. He set out to determine in his 199 patients the ratio of the number of headaches that were relieved by drug treatment to the total number of headaches the patients had in a two week period. He used drug agents 'A', 'B' and 'C' - and placebo. He called the rate of relief the "success rate." The subjects while being treated with three active drugs showed a "success rate" of about 0·8, that is, they reported that 8 out of 10 headaches were successfully relieved by the drug. When his 199 subjects were treated with placebos they reported a "success rate" of about 0·5.

Thus, there was a difference between the "success rate" with placebos and with active drugs, but it did not show which of the three drugs used was the most potent. The lower "success rate" with placebos was shown to be due to the fact that 60 percent of all the subjects consistently obtained relief from both placebos and active drugs, while only 40 percent obtained relief from the active drugs alone. The data was such that while differences between drugs A, B and C did not emerge in the "mean success rate," in the placebo non-reactor group drug A was found definitely more effective than the other agents.

Jellinek thus demonstrated two important effects. Firstly, that when placebo reactors were screened out more useful differentiations could be made than was otherwise the case. Secondly, that "the 120 subjects who reported relief at all through placebo did not do so only on one or two occasions, but rather consistently. Thus there are individuals who definitely tend to respond and individuals who definitely do not tend to respond to placebos." (Jellinek, 1946, p.88.) However, Jellinek came to a most odd conclusion after such an indicative study. He added, "this difference in response to placebo must reflect a difference in the nature of headaches." (Ibid). He elaborated that the sample was

drawn from at least two broad populations of sufferers from headaches. To him, if sufferers never reported relief from a pharmacologically inactive substance but always reported at least some attacks relieved through bona fide analgesics, it must be assumed that they reporesnted a "pure culture" of physiological headaches not accessible to suggestion, while the 120 subjects who either always or most of the time responded to placebo represented, perhaps predominately psychogenic headaches ... coupled with a tendency toward suggestibility.

Whatever his theoretical view point, Jellinek's study made it clear that as a consequence of the use of placebos, those who reacted to them in a positive way could be screened out to advantage under some circumstances and the focus sharpened on drug effects.

This was borne out by Beecher's report in 1953 that persons obtaining relief from placebos also got 58 percent relief from drug whereas only 34 percent of all people got relief from the placebo, when the effectiveness of oral analgesics and placebo for postoperative pain was compared. He concluded,

> "We cannot tell from this information whether the drug had an additional effect over that of the placebo on placebo reacting people. All we can say at present is that when the placebo reactors are taken out there are differential responses owing to drugs." (Beecher, 1953, p.398.)

He therefore recommended that an experimental population of selected placebo non-reactors be used in clinical investigations in order to permit demonstration of clear-cut differential responses to drugs. If such a selection of subjects were not made, it would be possible that effective agents might appear to be ineffective because of the "dilution" of data by the negative results obtained from tests in persons who might not be able to discriminate between active and inactive drugs.

2. The Work of Lasagna et al., 1954.

Beecher (1953) and Lasagna (1954) were responsible for the concept of the placebo reactor, and sponsored thorough investigation into the problem. His 1954 "Study of the Placebo Response" was prompted by Jellinek's work, but, in opposition to this writer, Lasagna thought there was a possibility that such individuals were psychologically predisposed to accept relief from drugs, whereas the non-reactors might by psychologically predisposed to resist such relief. Thus, in his work two important questions were raised: (1) Is the placebo reactor a recognisable type of individual? and (2) what are the outstanding psychological characteristics of the reactor?

Lasagna and his collaborators studied 162 patients who had undergone surgical operations. They devised a method of studying the effects of morphine and of saline on postoperative pain. In this way they were able to differentiate between placebo reactors and non-reactors.

Data consisted of (1) a standardised interview with each patient, designed to elicite past experience and attitudes which might be pertinent to the study; (2) questionnairs, evaluating the patients in regard to personality, staff - patient relationships and hospital course; (3) the Rorschach; (4) the Thematic Apperception Test; (5) an estimation of the I.Q. based on the Vocabulary sub-test of the Wechsler-Bellevue.

Compared to Jellinek's report that 60 percent of his 199 subjects received relief from a placebo on one or more occasions, Lasagna reported that only 30 to 40 percent of postoperative patients studied obtained relief of pain from an injection of saline. The uniformity of response was also greater in Jellinek's data since 69 percent of a special group of 120 subjects each receiving five placebo doses gave consistent responses (either positive or negative) whereas only 45 percent of the group reported in Lasagna's paper gave consistent responses. Jellinek thus had a U-shaped distribution for his frequency of relief, with a piling up of consistent, never-relieved

or always-relieved patients. Lasagna's distribution looked more like a normal curve.

There was no apparent difference between the placebo reactors and non-reactors as far as sex distribution was concerned, but Lasagna reported that the mean age for reactors was five years greater. Some of the indications of the data may be seen in Table I, reported by Lasagna, Mosteller, Felsinger and Beecher, 1954, p.773.

TABLE I. Mean Age, Medication Data and Duration of Surgery and Anaesthesia for Patients in Psychological Study (with Standard Errors)

	PLACEBO REACTORS (11)	PLACEBO NON-REACTORS (16)
Mean age, years	49.3 ± 2.2	43.7 ± 2.7
Mean no. of morphine doses per patient *.....	3.5 ± 0.7	5.5 ± 0.7
Mean no. of medications (morphine and placebo) per patient *.....	5.4 ± 0.6	8.6 ± 1.0
Mean pain relief from morphine *.....	95% ± 3.4%	54% ± 9.4%
Mean duration of anaesthesia (minutes)	215 ± 22	210 ± 24
Mean duration of surgery (minutes)	181 ± 21	177 ± 24

* Indicates significant difference ($p<0.05$) between reactors and non-reactors.

Lasagna published a further table in 1958, from this data, which showed, perhaps more clearly, the inverse relationship which existed between the number of doses of medication required post-operatively and the efficacy of morphine or placebo.

TABLE II. Pain Relief with Morphine or Placebo in Patients Suffering from Post-Operative Pain, from Lasagna et al., 1958, p.535.

GROUP		NO. OF PATIENTS	MORPHINE	PLACEBO
I	(2 doses/pt.)	12	92%	58%
II	(4 doses/pt.)	21	75%	40%
III	(6 doses/pt.)	15	61%	40%
IV	(8 or more doses/pt.)	15	58%	15%

In addition to this, Lasagna reported that placebo reactors tended to be more co-operative and sociable than non-reactors (as judged by the nursing staff) and were more likely to have somatic symptoms during times of stress than were non-reactors.

Rorschach responses were grouped to discover the largest combination that adequately differentiated the two groups. Six signs were common to 60 percent of the reactor group, while none of the non-reactors were so characterised. The six signs were: (1) more than one

"insides" response; (2) $\Sigma C > M$; (3) A% below 50%; (4) CF > FC; (5) more than two "anxiety" responses; and (6) less than two "hostility" responses. Reactors were shown to be more anxious and dependent, were more productive of responses, more self-centred and pre-occupied with internal bodily processes, and more emotionally labile. They were individuals who seemed more dependent on outside stimulation than on their own mental processes, and they seemed to have the ability to drain off their anxiety by means of their outward orientation, in contrast to non-reactors, who seemed to be more rigid and emotionally controlled. Additional information gained from interviews was that reactors were more regular churchgoers and had less formal education, but there were no I.Q. differences as measured by the Wechsler-Bellevue.

These investigators put forward the hypothesis that placebo reactors had a psychological make-up that predisposed them to anticipation of pain relief from any medication. They found no easily distinguishable personality differences between reactors and non-reactors, and less than half of the patients who received multiple doses of a placebo responded consistently to the placebo. This they advanced as evidence that all persons who will react consistently to placebo cannot be "screened" from

an unselected population by the administration of the placebo medication. Lasagna concluded that detailed study of a subject seemed to be necessary before he could be considered a priori, as a person likely to have a marked placebo response.

Finally, Lasagna warned investigators of the particular havoc placebo reactors could wreak in an experimental study in pharmacology.

> (1) That "placebo reactors may change the slope of the dose-response curve and in consequence the sensitivity of the experiment. (2) An effective drug may be wrongly discarded because data had been diluted by inclusion within the test group of a large number of placebo reactors, and (3) The optimal dosage of a standard drug may be underestimated if the placebo reactor group within the population sample is large and readily relieved." (Lasagna et al., 1954, p.770.)

Although Lasagna's study was of obvious importance, it contained many weaknesses. Some the experimenters admitted quite freely: for example, that the placebo reactions were only investigated in one type of situation (although this is hardly inescapable); that there was no objective measure of the drug effect or of the pain, which was presumably altering daily; and the psychological investigations were undertaken while the patients were convalescent, and may well, as Trouton points out (1957, p.348) "have not fully returned to their normal psychological state."

According to Trouton, some of the most relevant criticisms are firstly, that the assessment of personality was inadequate. No evidence was given on the reliability or validity of the questionnaire used to evaluate the patients in regard to personality, staff - patient relationships and hospital course, and Trouton especially claimed that there was reason to suspect the quality of the psychological information collected by the surgical nurses, because it was subject to their psychologically unqualified interpretation.

Trouton wrote that although the Rorschach seemed to differentiate the two groups significantly in certain ways, the composite portrait of the placebo reactors and non-reactors based on it was more questionable. According to Eysenck (1956a) when

> "used as a 'global' test of personality, subjectively interpreted and evaluated..... it appears to be almost entirely useless, and the experimental literature leaves little doubt that validation studies of the test used in this fashion nearly always give negative results," (quoted Trouton, 1957, p.349.)

although it may have some validity as a psychometric test objectively scroed. "The variable having the highest saturation on the introverted side" in a study reported by Eysenck (1956 b) was M%. Unfortunately, Lasagna and his collaborators did not mention this, nor the D score which is also said to be correlated with

extraversion. However, a high FM/M score was found to have a saturation of .50 on a factor identified as extraversion; it also occurred in twice as high a proportion of reactors. On the other hand a high F%, which also had a loading on extraversion was found in the non-reactors. So whether any conclusions can be safely inferred from the Rorschach procedure used by Lasagna remains doubtful.

De Maar and Pelikan, writing in criticism of Lasagna et al., in 1955, said

> "It should be emphasised too, that the short interviews were inadequate to diagnose placebo reactors in the group ..... It must be remembered that this study was concerned only with the behaviour of placebo reactors to the subjective response of pain. We must wait for other studies to determine whether placebo reactors show the same characteristic for other subjective and objective responses ..... The mechanism by which the placebo response is produced is still unknown. We have seen that the response to a series of administrations of placebos does not result in uniform responses to all the doses, even in a group of placebo reactors. It is possible that different mechanisms for the placebo response may exist in different persons or in the same person at different times. For example, in tests of hypotensive agents in hypertensive patients, placebo responses may take the form of either elevations or lowering of blood pressure. In other words, the response to a placebo may be either positive or negative." (pp.115-116.)

Their last point is well taken, even if the words 'positive' and 'negative' have awkward connotations. Lasagna's study allowed only for the inhibition of a response i.e. pain, and although we are not specifically told, patients, we must assume, were under the impression that what they were administered was a depressant, the function of which was to inhibit the pain response. As De Maar and Pelikan attempted to point out, the function of a placebo is not necessarily to inhibit. Results might have been different had a study been conducted on different lines without the subject's knowledge as to what type of drug it was they were taking, or, in a relevant situation, that they were receiving a stimulant.

However, De Maar's comment that the response to a series of administrations of placebos does not result in uniform responses to all doses, even in a group of placebo reactors, ignored the very clear data presented by Lasagna (see Table II) showing that the trend of consistency of response (or lack of it) is very similar for those patients on placebo and those on morphine.

3. Abramson et al., 1955.

In 1955 another study was undertaken by Abramson, Jarvik, Levine, Kaufman and Hirsch, but encompassing a set of circumstances somewhat different from those reported so far. The thirty-three non-psychotic volunteer subjects expected to get a dose of lysergic acid diethylamide which would produce "either a relatively mild or a relatively severe response, the severe response being in the nature of a temporary psychosis." (Abramson et al., 1955, p.367.) In the data therefore, there was no attempt to look for a sign of therapeutic efficacy, but only for the symptomatology of the structured psychological responses enumerated in a questionnaire. Using the terminology previously quoted from De Maar, Abramson said, "Our zero dose of LSD - 25 or placebo dose should be classified as a negative placebo because only symptomatic exacerbation may occur." (their italics, Abramson et al., 1955, p.368.)

Since LSD - 25 is tasteless, odourless and colourless the subjects could not detect that they were given 75cc. of tap water in lieu of the drug. A questionnaire, used to assess the responses, inquired about the subjects physiological and perceptual state.

PROCEDURE: Subjects were tested in groups of two to five. Some subjects in these groups received a placebo; some received the drug and exhibited "typical" LSD - 25 symptoms. Fifteen subjects responded to the questionnaire half an hour after receiving the placebo and at hourly intervals thereafter up to four and a half hours. Eighteen responded $\frac{1}{2}$, $2\frac{1}{2}$ and $4\frac{1}{2}$ hours after ingestion of the placebo; five subjects also responded before receiving the placebo.

The investigators related the number of different symptoms reported during these three intervals with the number of "yes" responses given on the Cornell Medical Index Health Questionnaire, the number of correct solutions on an Arithmetic test scores on the Rorschach, and the body weight of the subjects. The six "non-psychotic" subjects giving the least number of different responses during three time intervals were compared with the six "non-psychotic" subjects giving the greatest number of different responses during these time intervals. The scores of the two groups on each of the sub-tests of the Wechsler-Bellevue test, their Performance Scale I.Q., their Verbal I.Q., and their Full Scale I.Q., were compared. A third group of six subjects whose number of reported symptoms placed them in a "middle" symptom group was compared with the "low"

and "high" group to determine whether their scores on the Rorschach and Wechsler-Bellevue tests fell between those of the other two groups.

RESULTS: It was found that most subjects who responded to a placebo did so most markedly during the first half hour after receiving the substance. Abramson's conclusion was that at this time their anticipation of, and anxiety about, the effects of LSD - 25 were probably greatest. "Gradually the effects wear off as the anticipation wears off." (Abramson et al., 1955, p.380.) The questions eliciting the greatest percentage response were those relating to anxiety (moist palms and feeling anxious) or "to phenomena which commonly occur without the presence of any foreign agent (drowsiness, fatigue and headache.)" (Ibid.) The remaining questions received random responses.

A comparison of the "low" and the "high" symptom groups for the Wechsler-Bellevue can be seen in Table III below.

TABLE III. Comparison of "Low" and "High" Symptom Groups on Wechsler-Bellevue Intelligence Scale Scores, (N = 6 in each group) from Abramson et al., 1955, p.377.)

	AVERAGE SCORE		
ITEM	"LOW" SYMPTOM GROUP	"HIGH" SYMPTOM GROUP	p *
Verbal Scale			
Information	13.3	14.0	--
Comprehension	12.7	13.7	--
Digit Span	10.0	13.3	--
Arithmetic	10.2	15.3	.02
Similarities	14.5	14.5	--
PERFORMANCE SCALE			
Picture Arrangment	11.3	9.3	--
Picture Completion	11.3	11.0	--
Block Design	14.3	11.8	.10
Object Assembly	12.0	10.3	--
Digit Symbol	13.8	11.7	--
Verbal Scale I.Q.	116.8	128.5	.10
Performance Scale I.Q.	121.0	108.5	.10
Full Scale I.Q.	120.5	120.8	--

* - indicates that p is $\geq .10$.

It can be seen from Table III that the "low" symptom group showed a significantly greater ability to abstract and synthesise as measured by the Block Design sub-test. The "low" group showed a tendency to perform better than the "high" symptom group on all Performance Scale sub-tests but one (Picture Completion) and had a significantly higher Performance Scale I.Q. than the "high" symptom group.

The "high" group on the other hand showed a much greater ability to concentrate on and solve verbal arithmetic problems, as measured by the Arithmetic sub-tests. With the exception of the Similarities sub-test, the "high" symptom group tended to perform at a higher level on each Verbal Scale test, and in fact had a significantly higher Verbal Scale I.Q. So from this test it appeared that subjects in the "high" symptom group stressed a verbal or ideational approach in their efforts at adaptation, while the "low" symptom group subjects placed a stress on motor or performance functions in their adaptive efforts.

In addition, on the Rorchach test, the "low" symptom group was found to be much more stereotyped in its thinking and to emphasise the popular and conventional modes of responding, as measured by the popular response (P) variable.

Abramson therefore stated

> "It seems that it was the ideationally-oriented individuals rather than the primarily action-oriented individuals who demonstrated a greater amount of suggestibility, that is, a greater response to the placebo in our experiments." (Abramson et al., 1955, p.381.)

In addition, a correlation was shown between the average number of symptoms reported per hour by subjects at various dosage levels of LSD - 25. The correlation coefficient between the zero dosage group (i.e. placebo) and the 25 - 75 microgram group was ·66 (significant at the ·01 level); and the correlation between the zero dosage group and the 100 - 225 microgram group was ·60 (significant at the ·01 level.) (Abramson, Jarvik, Kaufman, Kornetsky, Levine and Wagner, Table 15, p.54, 1955.) This indicated that those subjects who gave positive responses under placebo did so under actual LSD - 25. This is in essential agreement with results reported by Lasagna et al., 1958, reported earlier. (cf. p. 37).

While Abramson's study had many advantages of approach in comparison to those already reviewed, it also suffers from some typical weaknesses.

The use of the Rorschach in Abramson's study must be queried on similar grounds to those mentioned in

criticisms of the work submitted by Lasagna (1954, cf. p.37) although it would seem that both workers, in interpretation of the variables elicited in response from the non-reactor groups, found some agreement i.e. that those subjects showing less reaction to placebo seemed more rigid, stereotyped and controlled. However, if we extract from their data the only variables they report which allow for comparison, it can be seen that there are obvious differences in their respective findings.

TABLE IV. A Comparison of Mean Scores Obtained on Three Rorschach Variables by Lasagna et al., (1954) and Abramson et al., (1955) for Placebo Reactors and Placebo Non-Reactors.

VARIABLES	ABRAMSON et. al			LASAGNA et. al		
	"HIGH" REACTORS	"LOW" REACTORS	p	PLACEBO REACTORS	NON-REACTORS	p
R	32.0	31.2	--	13.5	10.1	--
F%	85.0	85.8	--	41.6	64.0	.001
F+%	76.5	79.5	--	51.3	90.7	.001

Apart from the criticisms proferred as to the use of the test itself, possible sources of disagreement in these two studies might be due to the fact that the original sample selection was different, for Abramson

et. al., used paid volunteers, and it has become obvious that the personality make-up of the volunteer subject can bias resulting experimental data.

For example, this has been found to be the case in some studies of the personality traits of volunteers for interviews about sexual behaviour (Siegman, 1956.) Riggs and Kaess (1955) compared students who volunteered for a psychological experiment with those who had not; one of their findings was that the volunteers were significantly higher on the T and C scales of the Guilford S.T.D.C.R. questionnaire, "indicating respectively introversive thinking and moody cycloid emotionality." As Eysenck, (1953) has shown, both these scales are good measures of neuroticism, so that it appears probable that more neurotic subjects are more likely to volunteer for studies of this kind. This conclusion is strengthened by Lasagna et. al., (1954) from a study in which a remarkably high incidence of severe maladjustment was found among fifty-six volunteers for a drug experiment at Harvard Medical School.

It is noteworthy that no agreement was found when the results of the Wechsler-Bellevue were compared, for Abramson reported a significant difference between some sub-test scores, for "high" group reactors and "low" group reactors. Whereas Lasagna found no significant difference at all.

Like Lasagna, Abramson and his colleagues came to the conclusion that what had been measured was in some way "suggestibility." However, there would seem no adequate evidence that this was so.

It is difficult to agree with the conclusion that all those who responded to placebo were suggestible, because of the particular experimental procedure used. Firstly, all male experimenters were used, but the subjects were of both sexes. It is now known (cf. Evans, 1961) that an interaction effect between subjects and experimenters of different sexes can influence the measurement of suggestibility responses.

Also, it would seem that the method of testing the subjects in groups, and thereby allowing those on tap-water placebo to observe those actually on LSD-25, involved a subject interaction effect from cues being available which would destroy any measure of suggestibility per se.

It would seem that there was some lack of differentiation of anxiety as a pre-experimental personality trait. To report that the

questions which elicited the greatest percentage response were those related to anxiety is perhaps insufficient when it cannot be shown whether this was because those subjects who responded in such a way were normally anxious, independently of the experimental situation; or that the thought of taking LSD-25 made them anxious, in the specific experimental situation; or that the placebo reactors usually respond in this manner.

Finally, it is difficult to see why use such as this of a placebo should warrant the title of "negative placebo." Abramson claimed that it was labelled in this way because it was to have no therapeutic effect. However, this would seem excessive narrowing of the placebo concept. We might distinguish types of placebo reaction, but as can be seen from previous discussion, any reaction to an inert substance might reasonably be defined as placebo reaction. The term "negative" when used to describe the production of symptoms, as opposed to the alleviation of existing symptoms, seems to carry an unnecessary connotation of 'good' or 'bad' effect. We would rather maintain that any response to placebo should be accepted as such, and then classified to type where needed.

However, despite some disadvantages, the 1955 study was an advance in experimental flexibility of approach

to the study of placebo reaction, for it was the first time in which subjects had been studied in a non-therapeutic situation.

In 1956, Tibbetts and Hawkings briefly reported details of a controlled trial in which they compared the effects of intravenous acetylcholine and sterile water. They noted that about sixty percent of the patients improved, irrespective of whether the pharmacologically active or inert substance was used. The numbers were small and justified only impressions rather than conclusions, but it seemed as if youth favoured placebo response. There was little or no relationship between reaction and sex, I.Q. (the test was unnamed) and work record, presence of environmental problems, and severity of illness. However, "..... the presence of previous neurotic traits and hysterical or inadequate features in the personality militate against a positive placebo response." (Tibbetts and Hawkings, 1956, p.62.) Since the placebo reaction was generally accepted to be a manifestation of suggestion, the finding that it did not appear in hysterical conversion was at variance with the popular belief that there was a special relationship between hysteria and suggestibility. It was, however, in basic agreement with results reported by Eysenck, where after administering four tests of primary and four tests of secondary suggestibility to

sixty hysterical patients, " .... the conclusion was drawn that hysterics are no more suggestible than non-hysterics." (Eysenck, 1947, p.191.)

4. Studies by Wolf et al., 1957.

A different approach again to the problem was shown when in 1957, Wolf, Hagans, Doering, Ashley and Clark published two studies between them. Interest in the placebo reactor was aroused when they found that in two different trials with the same agent in the same individual, the protection afforded was equally inconsistent whether the agent was placebo or one of the drugs.

Twenty-six healthy young subjects were given ipecac, on each of two occasions. The incidence of nausea among these individuals was 100 percent on both occasions. Most of them vomited both times. On seven successive occasions, however, after a premedication with a placebo, the situation changed. Nausea failed to occur in many instances. During the seven trials with placebo premedication, it was found that all of the subjects at one time failed to become nauseated and thereby showed a placebo reaction.

> "The incidence and inconsistency of the protection responses observed with prior placebo medication were virtually the same with [a] 6 ml. and [a] 4 ml. [dose] of syrup of ipecac. This together with the fact that without prior medication the responses of the same subjects to the 6 ml. dose of ipecac were indistinguishable from those observed when 4 ml. was given, strongly supports the implication that the variations observed were not due to a difference in the size of the dose of ipecac but rather to the fact that the individuals respond inconsistently to the placebo. These findings do not support the concept of a placebo "reactor" who would be expected to respond in a consistent fashion to a placebo medication." (Hagans et al., 1957, p.284.)

These workers therefore began a more detailed consideration of this aspect of the data, with observations on the placebo reactor and non-reactor. The second study (Wolf et al., 1957) was undertaken to test the consistency with which placebo responses occurred from individual to individual and in the same individual from time to time.

Data from the earlier study of agents tested for their ability to prevent ipecac-induced nausea and vomiting showed that none was more effective or more consistent in its effect than a placebo (Hagans et al., 1957.) Since none of the agents showed evidence of pharmacodynamic activity, they were all regarded as placebos. The experimental group consisted of twenty-one volunteers who had consistently exhibited nausea upon the

ingestion of ipecac alone on two separate occasions, and fourteen who had consistently exhibited vomiting. Each underwent seven additional trials with ipecac preceded by oral administration of the agents according to a double-blind systematised randomisation technique. Both the subjects and the investigator were aware that an antiemetic effect was being sought. Following each of their seven trials, a subject's failure to develop the anticipated nausea and/or vomiting was designated as a placebo response. Those who consistently displayed placebo responses or consistently failed to do so were called pure reactors or non-reactors respectively; those who displayed placebo responses on exactly half the trials were called half-reactors; and those who had more placebo responses than non-responses, but were not totally consistent, were termed impure reactors (or impure non-reactors if they demonstrated more non-responses than responses.)

Wolf claimed that these data were particularly suitable for testing the concept of the placebo reactor because both a "subjective response" (nausea) and an "objective response" (vomiting) were observed. Since the number of the tests performed on each subject was seven, the subjects were divided into groups of seven and each was analysed from three standpoints.

The distribution of complete "protection" against nausea in the twenty-one subjects and of complete "protection" against vomiting in the fourteen subjects, as well as the distribution of partial "protection" against either nausea or vomiting, was recorded and compared to the theoretical distribution attributable to chance, as derived from the binomial expansion equation. The data showed no significant difference between the observed results and chance.

Further, the total of all placebo responses in the thirty-five subjects was compiled and compared again to the appropriate chance curve. Again there was no difference between the observed results and chance.

Finally, the variation in the occurrence of placebo responses from time to time in the same individual was compared with that observed from person to person. It was found that the curves for variation in placebo response, both inter- and intra- individual, did not differ from each other or from chance. In each instance the data was subjected to chi-square analysis which established lack of any significant differences.

The next question involved an attempt to establish whether or not the occurrence of a placebo reaction had predictive value with respect to the likelihood of that individual displaying further placebo reactions in the

future. The incidence of placebo reactors and non-reactors, pure and impure, and half-reactors on the basis of the first test alone, the first two tests, and so on up to and including all seven tests was studied. There was essentially a 50:50 distribution of reactors and non-reactors when an off number of tests were analysed, and a 33:33:33 distribution of reactors, non-reactors and half-reactors when an even number of tests were analysed. The pure placebo reactor virtually disappeared from the group after the sixth successive test.

Wolf et al., wrote that it was not possible on the basis of 1, 2, 3, 4, 5, or 6 tests to predict whether or not an individual would display a placebo response on subsequent testing. Further, the pure reactors, even when defined on the basis of five previous successive placebo tests, showed no greater incidence of subsequent positive responses than when defined on the basis of 1, 2, 3, or 4 previous tests. The incidence of reactors, non-reactors and half-reactors was examined on the basis of the first test compared to the last test, the first two tests compared to the last two tests, and then the first three tests compared to the last three tests. The break-up of groups can be seen in more detail in Table V. The individual

consistency was also examined for each of these groups, comparing the first to the last test as above. No significant differences occurred and the consistency of responses was nowhere greater than could be expected to occur by chance.

TABLE V. The Incidence of Reactors, Non-Reactors and Half-Reactors as quoted by Wolf et al., 1957, p.841.

	REACTORS	NON-REACTORS	HALF-REACTORS	CONSISTENT RESPONSE
FIRST TEST COMPARED TO LAST TEST				
First	19 (54%)	16 (46%)	0	18 (51%)
Last	18 (51%)	17 (49%)	0	
FIRST TWO TESTS COMPARED TO LAST TWO TESTS				
First 2	12 (34%)	10 (29%)	13 (37%)	11 (31%)
Last 2	15 (43%)	10 (29%)	10 (29%)	
FIRST THREE TESTS COMPARED TO LAST THREE TESTS				
First 3	17 (49%)	18 (51%)	0	20 (57%)
Last 3	22 (63%)	13 (37%)	0	

Finally, Wolf and his collaborators concluded that,

> "these data do not support the concept that either a placebo reactor or a non-reactor really exists as a separate or distinct entity in an experiment measuring an objective phenomenon (vomiting) and a subjective phenomenon (nausea) or even with respect to the potentially more highly suggestible partial relief of nausea and/or vomiting. Since the intraindividual variation in response to a placebo was found to be as great as the interindividual variation, the likelihood of predicting placebo responses was not enhanced by increasing the number of placebo tests performed on any individual." (Wolf et al., 1957, p.841.)

There are obvious discrepancies in the studies reported from 1946 until that of Wolf in 1957. Wolf advanced the hypothesis that the differences in conclusions implied from the studies of the various workers

> ".... may be reconciled in view of the evidence that placebo reactions depend upon the particular circumstances prevailing at each administration. Relevant among these would be the nature of the symptom being treated, the motivation of patient and physician, the nature of the test agent, its mode of administration, and the life situation of the subject at the time he is tested. The significant point here is not the apparently conflicting findings of investigators with respect to placebo reactors, but rather that in any given situation, responses to a placebo may

> vary as compared to any other situation and the significance of situations to human subjects cannot be precisely duplicated. Therefore, it seems unlikely that a placebo reactor can be identified and eliminated from an experimental situation on the basis of evidence gathered from some other situation. Rigorous placebo control will probably continue to be necessary in therapeutic research." Wolf, 1959, p.700.)

Although a reasonable comment, this might be viewed as overly pessimistic. Many factors other than those mentioned by Wolf could account for differences. Not the least of which would be weaknesses in his own study, where for example, a response had to be inhibited i.e., vomiting had to be stopped. This is somewhat different from producing an effect, as in Abramson's case. The expectation and study of response inhibition raises difficulties, such as the question of whether the subjects are <u>capable</u> of inhibiting these responses, involving individual differences (cf. Eysenck, 1957.) Also, there is the question of whether the capability may be related to any other factor not included as a possibility by Wolf.

If an interaction situation was involved between those administering the placebo and those receiving it, as Wolf suggested, then he allowed for an unfortunate magnification of the problem in the experimental design,

by the use of four different experimenters in interaction with subjects of both sexes. No account was taken of this as a possible factor influencing the inconsistency of results, although, as stated earlier, it is known that the experimenter-subject influence and relationship can be of the utmost importance.

In this vein, it cannot be entirely said that the subject is not responding to the placebo when no response is elicited. There remain the factors of the inner state of the subject, the timing of the stimulus presented, and the reinforcement of this stimulus. The reinforcement of the stimuli by various experimenters, and the additional presence of extraneous stimuli could account for the lack of uniform responses.

Also, there is the possibility of an extinction of the placebo response over time. Lasagna's important work (1958) showed that there was an extinction of response to active drugs over time, so it seems quite possible that a similar result could be gained from placebo response, rather than labelling lack of response, or decline in response, purely 'inconsistency.'

5. The Work of Gliedman et al., 1958.

A final study in this series was undertaken in 1958 by Gliedman, Nash, Imber, Stone and Frank. The original research programme consisted of an opportunity for six months of psychotherapy with intensive evaluations initially; at the completion of treatment; after another six months; and at yearly intervals thereafter. Inert medication was made available two to three years following the patients' first contact with this project. Instructions were given to take the tablet preparations orally, four times daily for a period of two weeks, as a hopeful means for the reduction of verbalised distress. None of the patients knew they were being given inactive preparations. No psychotherapeutic contacts were had during the placebo trial interval.

The same discomfort scale used to reflect patient changes in psychotherapy and at the times of follow-up was employed to study the response to inert medication. This inventory was made up of forty-one items of somatic and psychological distress, each of which was rated by patients on a four-point scale. Other data presented for these patients were suggestibility scores derived from a sway test administered prior to the patients' experience of psychotherapy; replies to a specially prepared questionnaire designed to assess orientation to

medicine and physicians; and responses to a test of 'temporal orientation.' The discomfort scale was administered before and after completion of the two week trial of placebo, and the scale was used to divide the sample of fifty-six patients into placebo reactors and non-reactors. The twenty-eight placebo reactors were then compared with the twenty-eight non-reactors. A slight tendency was noted for the reactor group to have less education, to be younger, and to have a larger number of female patients. No significant differences were apparent with regard to marital status. There were significantly more diagnoses of anxiety and depression among the reactors ($p < .05$) than among the non-reactors.

In the questionnaire pertaining to orientation to medicine and physicians, twelve questions were found to have value in differentiating the reactors from the non-reactors. The reactors reported more experience with minor sickness, seemed to place more value on medicines and physicians as distress relievers, appeared to recommend actively what he found helpful, for others, and believed himself to be a religious person who regularly participated in his Church's activities.

Twelve former psychotherapy patients who received placebo showed some order of symptom reduction following placebo as following psychotherapy. For this group, no

age, sex, marital status, education or social class differences were noted among reactors and non-reactors. Likewise the past ratings of suggestibility on body sway did not differentiate between the two categories of patients.

On the test of temporal orientation, there was a tendency for the reactors to be present avoidant. They scored primarily in the two other time dimensions, past and future, as was consistent with the diagnoses of anxiety or depressive reactions found.

Gliedman and his colleagues concluded that,

> ".... the tendency to respond to placebo is a highly desirable attribute for recovery," (Gliedman et al., 1958, p.349.)

and went on to add,

> "The scanty follow-up results indicate that the effects may not be maintained. They do not indicate that psychotherapeutic approaches and placebo approaches in this clinic share something in common, as indicated by Rosenthal and Frank (1956) and that the nonspecific therapeutic forces involved are part of every procedure especially the administration of drugs, as emphasised by Modell (1955.) The importance of expectancies is apparent even in conditioned reflex experiments with animals, and emphasises the fruitfulness of considering the so-called placebo effect from the standpoint of prior learned experiences which dispose to certain favourable present actions, as pointed out by Gliedman, Gantt and Tietelbaum (1957.)" (Ibid.)

It is also of note that suggestibility, which seemed to the majority of workers to be involved in response to placebo, seemed unrelated to the reaction, as measured by the body-sway test.

In a survey of the experimental work reported, despite the results of Wolf, the majority of studies confirmed some consistency of placebo reaction -- indeed, enough for workers in the field to write of and accept the implication of a "placebo reactor." In 1957 Trouton wrote,

> "Possibly the consistent reactors represent the two extremes of a personality continuum with the majority falling in between as with so many other psychological traits. But the low degree of consistency, even under the carefully controlled conditions of the experiment, suggests that it might be difficult to obtain any consistent reactions at all if subjects were compared in several different situations. The specificity or generality of the placebo reactions might well be determined before attempting to correlate the supposed trait types of personality. It is possible that the patients who obligingly improve on a placebo are not the same as those who contrive to develop those curious and sometimes even alarming symptoms which have sometimes been reported to occur." (Trouton, 1957, p.347.)

STUDIES CONDUCTED ON REACTORS TO ACTIVE DRUGS

With so few indicative studies on the placebo reactor, it might be well to turn briefly to the studies conducted on reactors to active drugs, since it has been shown that responses to placebo replicate those which are legitimate pharmacologically. Kornetsky and Humphries (1957) found that subjects with high scores on the Depression and Psychaesthenia scales of the M.M.P.I. responded with maximum subjective changes after chlorpromazine, meperidine and LSD - 25 or secobarbitone. It was surmised that there were reactors and non-reactors to drugs of whom the reactors were likely to be individuals who were depressed and/or likely to experience unreasonable fears, as well as to over-respond to environmental stimuli. Felsinger et al., (1955) believed that subjects with abnormal personalities responded atypically to amphetamine and morphine.

Dickel and Dixon (1957) linked the presence of anxiety with adverse response to drugs. Their conclusions were novel in that they pointed to the adverse effects of drugs hitherto considered most suitable for alleviating anxiety, and although Kornetsky et al., (1957) had indicated a possible dichotomy between the objective and subjective effect of a drug making it impossible to predict accurately the extent of one from the other, the

fact that so many anxious individuals developed physical signs with tranquillising drugs reflected doubt on Shagass'(1958) contention that anxiety could be equated with a high sedation threshold and that only one personality dimension (introversion - extraversion) was linked with drug susceptibility.

Earlier reviews of the psychological effects of drugs were made by Poffenberger (1914, 1916, 1917, 1919), Meyer (1922), Darrow (1929), Spragg (1941), Gray and Trowbridge (1942.) This work has been commented upon by Eysenck (1957) as not forming part of the theoretical system and not leading to any rational prediction. Similar 'censure' was passed by Trouton (1958.)

Work such as Eysenck's accepts for its creed that variable response to drugs may be in part and even a major part, determined by personality. Such a theory, to be comprehensive, must be able to explain phenomena such as a drug specificity, tolerance and susceptibility. After work in 1960 Eysenck was able to report,

> "Susceptibility to these drugs [meprobamate and Doriden] appeared to be a constant personality feature, and correlations of this susceptibility with Extraversion and Neuroticism were found, although not at a statistically significant level." (Eysenck, 1960, p.233.)

From this summary it can be seen that as much work is needed on the reactor to drugs as on the reactor to placebos and it must be recognised that the two approaches are by no means opposed or unrelated. Questions need to be raised and answered, such as the matter of determining the factors in any particular individual which alter the responses to the drug in question from time to time. Answers to such questions help us to understand why an agent may fail to work at one time or produce more effect than anticipated at another.

THEORIES ADVANCED TO EXPLAIN PLACEBO REACTION

From the work reviewed on placebo reaction, it is obvious that whenever placebo was administered, measurable changes at end-organs were always demonstrated. The genuineness of the phenomenon is without question. The next step is then, obviously, to ask what sets off the neurohumoral mechanism presumably responsible for these changes. There are several types of theories advanced to explain placebo reaction.

1. Theories Using the Concept of Suggestibility

It was accepted for some considerable time (and still is, quite extensively,) that suggestion was the sine qua non of placebo reaction, the effectiveness of the placebo being directly proportional to the degree of associated suggestion in the situation. This attitude has been fostered by such as the interesting report, in a converse situation, by Wolf and Wolff (1947) that the 'suggestible' patient under-reacts to large doses of a potent drug when under the impression that he is receiving a placebo.

Discussion of the placebo effect during the nineteenth century revolved around the concept of suggestion. This was stimulated by the advent of 'magnetic' and 'hypnotic' treatment, and by Bernheim and Liebault's assertions that hypnosis was a particular state of intensified suggestibility brought about by

suggestion itself. This was taken up by the Nancy School, which maintained that hysteria was a manifestation of hyper-suggestibility to endo-psychic stimuli, just as hypnosis was the result of hyper-suggestibility to exo-psychic stimuli. As pointed out by Janet, (1924, 1925) there was a long period of "miraculous healing" in which cure was attributed to gods. A "metaphysical stage" followed in which power was invested in a particular person and exemplified by Mesmerism and Christian Science. The "Scientific Stage" (Bernheim, 1890; Janet, 1924, 1925) followed with the advent of hypnotism. "These stages stamped their character on discussions of what is now called the placebo effect." (Shapiro, 1960, p.126.)

Levine, writing in 1942 in his text book on medical practice, summed up the general attitude by including a discussion on the placebo in his chapter on "Suggestion Therapy." He added that as a therapeutic measure, it

> ".....is one which occasionally can be useful ..... (and) ..... patients with psychiatric symptoms occasionally can be helped by medicine as psychotherapy."
>
> "..... cases in which the patients do not permit us to remove the source and still other cases in which we cannot remove the source, it is a legitimate procedure to give the patient medication, which has a pharmacologic effect and in addition has a psychologic effect." (quoted Shapiro, 1960, p.202.)

Viewed as a method of suggestion therapy however, objections to the use of placebo were numerous (cf. Diethelm, 1936; English, 1936; Salifield, 1953; Masserman, 1955.)

Of all the studies reviewed earlier, only one, (Gliedman et al., 1958 see p.63) attempted to verify experimentally the common belief that suggestion was involved in placebo reaction. The use of and approach to the problem of suggestibility in this context was, however, carried out with some disregard of the more recent advances and problems in the field of suggestibility theory. It is inadvisable to draw more than tentative conclusions from the use of only one test of suggestibility (the body-sway test) and this was administered under some difficult conditions. For example, five different experimenters were used, and the test was given a considerable period before placebo reaction was measured. This tends to conflict with the evidence of Evans, 1961, that there is a certain amount of retest unreliability attached to the body-sway test. This probably was a partial cause of the fact that experimenters in the field ignored the rather interesting result that no relationship was found to exist between suggestibility and placebo reaction.

Trouton (1957) was the first to put forward tentative hypotheses as to the relation of suggestibility to placebo

response. Eysenck (1943, 1947), Furneaux, (1945, 1948) and Eysenck and Furneaux (1945) had argued that there was no general unitary trait of "suggestibility." Two factors, possibly more, were necessary to account for the inter-correlations between tests traditionally associated with measures of "suggestibility."

The main factor, which was labelled "primary suggestibility" involved the person receiving the suggestion stimuli responding to direct (verbal) suggestions of the occurrence of specified bodily or muscular movements without his active volitional participation. The Body Sway and Chevreul Pendulum tests are familiar examples.

The second factor delineated was a more elusive concept. It involved "indirection" and "gullibility." Eysenck has described it as "the experience on the part of the subject of a sensation or perception consequent upon the direct or implied suggestion by the experimenter that such an experience will take place, in the absence of any objective basis for the sensation or perception." (Eysenck, 1947, p.167.) The Ink Blot, Progressive Lines and Odour Test were cited as typical examples.

Trouton, in view of Eysenck's work, claimed that "if placebo reactions are manifestations of primary suggestibility, which is closely related to neuroticism,

it would be expected that hysterics would differ from the normal in the same direction as dysthymics, although possibly to a lesser degree." (Trouton, 1957, p.350.)

He went on to add that it seemed more likely that secondary rather than primary suggestibility was the trait related to placebo reactions in so far as these are not learned. Primary suggestibility is related to movements, whereas

> "the main feature in the tests which go to define this trait (of secondary suggestibility) is the experience on the part of the subject of a sensation or perception consequent upon the direct or implied suggestion by the experimenter that such an experience will take place in the absence of any objective basis for the sensation or perception." (Eysenck, 1947, quoted Trouton, 1957, p.350.)

Trouton continued, "This might almost be taken as a definition of a placebo reaction. It should be relatively simple to test this theory." (Trouton, 1957, p.350.)

To test the theory is obviously necessary, but recent work on Eysenck's results would seem to indicate that caution must be exercised before doing so. Administering fifteen suggestibility tests which were similar to those used by Eysenck and Furneaux, to sixty-three undergraduates, Hammer, Evans and Bartlett

(1961) reported two orthogonal factors from a factor analysis of the tetrachoric correlations. One factor was obviously identical with the concept of "primary suggestibility," but there were no grounds for identifying the second factor with Eysenck's concept of "secondary suggestibility."

The recent work of Hilgard, Weitzenhoffer, Landes and Moore (1959) strongly suggests that primary suggestibility is not a unitary trait, perhaps not even factorially homogeneous. They present correlational evidence which suggests that the passive acceptance of primary suggestion of the Body Sway and similar tests in qualitatively different from challenging suggestions of an inability to resist a movement or inability to carry out a specified movement.

Evans, (1961) in a critical re-analysis of Eysenck's original data, found three main factors, labelled A, B and C. Factor A confirmed Eysenck's interpretation of Primary suggestibility, but Evans reported of Factors B and C, that there appeared to be no basis for identifying either of the remaining factors with the concept of "secondary suggestibility" defined by Eysenck (1947.) Factor B saturated significantly only three of the six tests of so-called "secondary suggestibility" and Evans claimed that Factor B was not the more subtle prestige-type

factor that Eysenck described, but a mixture of command authority blended with prestige.

Any work undertaken to relate suggestibility to placebo reaction must obviously take into account these later and more subtle developments since Eysenck first published his findings.

As yet, only one study appears to have been carried out which is at all relevant to it. Grimes (1948) included a "placebo" test in a battery of tests of suggestibility, as a test of prestige suggestibility. Unfortunately its test-retest reliability was low (·43) and its correlations with the other tests insignificant. Secondary suggestibility has not been related to any personality dimension. The aptitude for it may be affected by the attitude as Eysenck (1947) found with primary suggestibility, and this could account for an individual difference in response between co-operative dysthymics and actively indifferent hysterics.

It can be seen that much more detailed and sophisticated approaches are needed in studying the relationships involved between suggestibility theories and placebo reaction.

2. Theories Using the Concepts of Belief and Expectancy

This approach also overlaps the problem of belief. There are several kinds of content of belief in a clinical or therapeutic situation. Firstly, that certain effects will result. Secondly, in the therapist-figure as a source of help. Thirdly, in the technique, as a source of help.

Belief presupposes that the patient has some idea what effects he wishes to result, it entails dependency; it entails belief in disembodied "procedures" as the location of means to the resolution of felt difficulties; and belief is unspecified. There is no point in measuring the degree of belief without specifying the content of the belief. We must also distinguish between belief as faith, credulity or over-readiness to accept, and belief as intellectual assent. If it were supposed that the results of investigations permitted the conclusion that degree of improvement in placebo therapy was strongly related to degree of produced belief, the distinction between faith and intellectual assent then required examination of the following question: which comes first, a change in belief, or a change in the patient's behaviour?

Belief and expectancy are similar and it was Frank in 1960 who hypothesised that it was the symbolic

meaning of the placebo medication that was important. He pointed out that the symbolic meaning may not always be favourable, for some patients fear drugs and distrust members of the medical profession. He claimed that,

> "If the effectiveness of the placebo lies in its ability to mobilize the patient's expectancy of help, then it should work best with those patients who have favourable expectations from medicine, and, in general, accept and respond to symbols of healing. It appears that the ability to respond favourably to a placebo is not so much a sign of excessive gullibility, as one of easy acceptance of others in their socially defined roles." (Frank, 1960, p.70.)

An experiment which demonstrates the approach tendered by Frank, was conducted by Kast (1959). Twenty patients suffering from an anxiety syndrome with gastrointestinal sensitization were the subjects. The study's purpose was to test the efficacy of meprobomate and the antispasmodic agent tridihexethyl iodide, by presenting to the subjects a "consistent and at times deliberately varied attitude of the doctor and observing closely the subjects' interpretation of this attitude." (Kast, 1959, p.234.) The drug was given "with enthusiasm" for six weeks. A placebo then replaced the drug and the positive attitude was maintained for five weeks. In the third phase the drug, differing in physical

appearance from the initial phase, was given for six weeks, with an accompanying "negative attitude," by the physician. The results indicated that the medical environment, including the patients' interpretation of it, "exerted a deep influence" (Ibid) on the efficacy of even a potent drug. A similar influence was noted with the placebo.

3. The Theoretical Contribution of Beecher (1956)

Although concerned with the situation and the subjects' expectations, Beecher's conclusions (1956) were comewhat different. He summarised his convictions as the result of several years study of the placebo problem by observing that the important factor in the "stimulus-suffering sequence" is a person's reaction to sensation. The action of a placebo or of a drug which alters subjective responses to painful stimuli is through a modification of a reaction to an original sensation, rather than by direct effect on the original sensation itself. Beecher wrote,

> "Placebos.....appear to be more effective when the stress is great than they are when it is less, both for subjective and objective responses. Assuming that the significance of stress increases with the degree of stress, the results of the present study and of Cleghorn's study [1950] seem to indicate that the significance of stress, pain in the one

> case, anxiety in the other, determines the extent of the placebo effect. If this is true for placebos, one must entertain the view that the degree of effect of "active" drugs (surely in so far as they have a placebo component) may be influenced by the severity of the symptoms for which they are administered." (Beecher, 1956, p.168.)

This appears a feasible concept, but is of course limited to specific situations where placebo is administered as a therapeutic measure to dispel distressing symptoms. It has been seen that there are many other situations in which placebo is administered with a resulting placebo response, and Beecher's hypothesis that stress or anxiety are correlated with reaction must be tested under differing circumstances.

4. Theories Using a Conditioning Model

Gliedman et al., (1957) introduced an approach in terms of a state of central excitation induced through conditioning. He agreed with Beecher that placebo reactivity in humans was directly related to experienced distress, and claimed that this was a further demonstration in humans of the importance of the state of the organism. He translated Beecher's theories into a conditioning model by considering the strength of the unconditioned response as representing the state of the organism from the standpoint of distress.

He wrote,

> "It is known (Gantt, 1944) that the intensity of the elicited conditioned response varies exponentially with the size of the unconditioned stimulus which elicits the unconditioned response (or distress) the greater the conditioned response and possibly the more accessible is an organism to modification by a variety of means including placebo." (Gliedman et al., 1957, p.1107.)

Gliedman indicated experimental work which seemed to show that the meaning of a person to the animal, as experimental subject, could have profound effects on the reactions which appear, and that these meanings are probably outgrowths of the animal's past experiences which have been incorporated into his repertoire of reaction tendencies. Gliedman suggested that this was a prototype, in an oversimplified fashion, of what might occur in human situations.

> "The impact of the doctor on the patient can be such as to modify or worsen the disease depending to some degree on the meanings the patient has learned about certain or all help-giving situations in the past ..... When placebos are employed, the achieved changes in a patient's status may reflect his response to the particular doctor as symbolised by the medication, regardless of whether it was pharmacologically active or not." (Gliedman et al., 1957, p.1105.)

He proposed a state of arousal, presumably central in nature, as explanation. This state of arousal could

cause the patient to become accessible to the doctor's expectations of him. On the other hand, he viewed an alternative explanation as that a patient might try to meet his doctor's expectations because of anticipated rewards from him such as approval, respect, understanding etc., provided the doctor meaningfully arouses him, i.e. provides an appropriate central excitatory state. The use of placebo in these circumstances might function to reinforce symbolically such a doctor's effect in terms of the rewards the patient receives for modifying himself in accordance with his doctor's implied or direct recommendations.

It was thought that "toxic" reactions in patients might be explained on the basis of the impact or effect of the doctor on the patient. If a doctor is anxiety-producing because of a patient's past experience with similar figures, and this patient already suffers from an anxiety-reaction, then this particular doctor-patient relationship might lead to a worsening of the patient's condition.

He concluded,

> "The presence of recovery processes is obviously of extreme importance in the determination of placebo effects in patients ..... where animals or humans can react to their own deviations from homeostasis and where these deviations set off restorative processes, therapeutic

> invention, including placebo, has an already existing substrate of recovery for exploitation." (Gleidman et al., 1957, p.1106.)

Continuing a learning theory approach to the problem, Trouton (1957) suggested that when repeated doses of a drug and/or placebo were given, the effects of learning and discrimination would be expected to become more pronounced. Glaser and Whittow (1954) found that subjects receiving placebos reported more symptoms if they had been given a drug of similar appearance a few days previously, than if they had not received any previous medication. In succeeding test, the incidence of symptoms, reported after placebos declined. Even filling in questionnaires (as well as the taking of tablets) according to Glaser and Whittow, can give rise to apparent responses in man. However when the procedure of administering placebos, and scoring symptoms by means of questionnaires was repeated at intervals of from two to five days, the responses became progressively less by about twenty percent until the third test, after which they reached a steady level. They wrote,

> "If a drug, indistinguishable from the placebo is now given, it appears to have an inhibiting effect on whatever habituation may have been acquired, because in the following test (when

> dummies were given again) more symptoms were recorded than before the drug had been taken." (quoted Trouton, 1957, p.351.)

Trouton maintained that a tentative explanation of these findings might be given in terms of learning theory. The initial responses to the placebo-questionnaire situation might be regarded as the result of generalisation from other learning situations; the diminution of responses to this situation on repetition, as the result of lack of reinforcement; and the increase in responses to the placebo-questionnaire situation after a drug had been given, as the result of disinhibition.

It is difficult to agree with Trouton's reasoning in the light of Glaser and Whittow's study, which pointed to a levelling-off stage of response to placebo. Also, in contradiction to Trouton's argument we must refer again to the work of Lasagna (1958) which showed that response to placebo decreased in proportion to response to an active agent.

Trouton went on to assert,

> "Although the individual differences in these responses have not been related to personality, if the above elementary interpretation in terms of learning theory is tenable there is at once a hypothetical link with personality theory. According to Eysenck's (1955)

> theory concerning the basis of differences between introverts (and dysthymics) and extraverts (and hysterics) it would follow that the introvert would tend to acquire placebo responses more readily and to lose them less readily than the extravert." (Trouton, 1957, p.351.)

Thus it can be seen, in surveying the major theoretical approaches offered, that many workers are in basic agreement that attitudes on the part of the experimenter and the subject are important in the production of the placebo response, and can be even expressed as a learning theory model. However, mere conjecture is still all that can be offered about the relationship of personality traits as compared to the effect of environmental variables on placebo reaction. In addition, little satisfactory work has been attempted in this area. It is obvious from criticisms of the studies reviewed that lack of a co-ordinated approach amongst experimenters has ended in conflicting and confusing results. No adequate theory may be advanced under these circumstances. In addition poor presentation of results by many has made any clear cut picture difficult to obtain.

THE NECESSITY FOR RESEARCH

With the appearance of scientific foundations under medical practice, questions about the placebo become pressing. How does it work? On what does it work? On whom does it work? In drug research the placebo of course plays the indispensable part of the "control." Many questions however, arise concerning the nature and efficacy of such controls which cannot be answered without extensive research in which both physiological and psychological factors must be taken into account.

Although it has been shown that the use of the placebo is not new, the wide variability of its effect and the factors influencing this variability remain relatively unexplored areas. As a consequence, most of the reports surveyed consisted merely in the citing of such an effect, with little or no additional information being offered to account for the underlying psychological and physiological variables involved. Not only are the relationships between these variables and degree of placebo reactivity a clouded issue, but also the problem of the duration of reactivity and the extent of its arousal are equally undefined.

It is accepted by all research workers that methodological errors determining the results of experiments

can result from variables other than the experimental ones. (cf. Orne, 1959.) These errors can arise at any and all stages of an experiment. If the experimental group is not compared with a control group which has been matched, randomised or analysed for age, sex, acuteness or chronicity of illness, length of hospitalisation, diagnosis, prognosis, psychodynamic states and a great number of other variables, then the experimental results are very likely to be erroneous. The use of the placebo in pharmacological studies shows the concern of the investigators with these problems. However, the effect of the placebo when it is an uncontrolled variable in experimental research or therapeutic evaluation can become subject to these methodological errors.

Thus a clarification of the placebo effect requires that a distinction be made between methodological variables, the placebo effect itself, and the placebo effect as an uncontrolled variable. In addition, as pointed out by Fischer (1956) the placebo should be distinguished from the placebo effect; the placebo being the agent which may or may not result in a placebo effect.

Preliminary investigations are needed on a population which is to serve as a source of information

for drug trials and it is desirable that an evaluation be made of the magnitude of the placebo response likely to be encountered. Such data may be helpful in deciding how much attention is to be devoted to the phenomenon. It appears reasonable to assume that on the basis of the reviewed evidence that the higher the incidence of placebo reactors, the greater the dilution of the desired data, and the more important the screening of subjects. The employment of single doses of placebo to "label" subjects as "reactors" or "non-reactors" is at best only a partial solution to the problem.

If there are at least two classes of persons distinguished by their response to placebo, and as placebo reactors respond in large part to drug administration per se, while the placebo non-reactors seem to discriminate better between drugs and dosages, it would seem reasonable to adjust dosages and evaluate drugs on the basis of those patients who can discriminate, unless other considerations rule against such a procedure. It has been shown that placebo reactors change the slope of the dosage-response curve and in consequence the sensitivity of an experiment. Also, placebo reactors, by their high relief rate, mask gains from a drug as compared to the non-reactors. Only by separating placebo

reactors from the non-reactors can experiments be made more efficient in terms of reducing the number of observations. In addition, the subjective effects of drugs can be quantified accurately only when the placebo reactors are screened out. (Beecher, 1952.)

The proper formulation of a question constitutes more than half the answer, and wherever the effects of chemical treatment are being assessed, with the present stage of knowledge, many questions are in the unanswered category. For example, it must be asked, is the reported effectiveness of a new method of treatment primarily the result of enthusiasm or the placebo effect?

There exists a definite danger that any newly developed treatment technique may produce positive results due to factors other than those involved in the technique itself. The belief of the proponents of the treatment may convey itself to the patients and both the judgement of the observer and the response of the patients be thereby influenced. There exist certain factors to-day that tend to favour the occurrence of such an event.

Firstly the climate of opinion is such that a biochemical or physiological explanation or technique of treatment would be welcomed. Because of the general desire for this type of explanation there must be

extreme caution of uncritical agreement.

The second factor favouring the acceptance of such theories (regardless of their validity) is the tremendous need for new types of treatment. In the past there has been no treatment that has materially reduced the mental hospital population and with the increasing accumulation of patients the search for such a treatment is intense. Because of these factors there is considerable need for research into the problems surrounding this area of investigation.

Similarly, psychotherapists have theories of personality and psychotherapy and plan their therapeutic actions in the belief that these are the active agents which produce the desired results. Any favourable changes in patients consequent to a course of psychotherapy tend to be cited as evidence for the validity of the theory of personality and neurosis which underlies the rationale of the psychotherapy. In view of present knowledge of the placebo effect it may well be that the efficacy of any particular set of therapeutic operations lies in their analogy to a placebo in that they enhance the therapist's and patient's conviction that something useful is being done. Patients entering psychotherapy have various degrees of belief in its efficacy, and this may be an important factor in the results of therapy

though it has attracted little study. (It may be pointed out parenthetically that conviction of the helpfulness of therapy need not be equated with "motivation for therapy" which was investigated by Grummon (1954) and Dymond (1955) and found to have little relationship to success in psychotherapy. Patients are often sufficiently distressed to be strongly motivated to receive help, yet have little faith that a procedure such as psychotherapy can help them.)

The similarity of the forces operating in psychotherapy and the placebo effect may account for the high consistency of improvement rates found with various therapies, from that conducted by physicians without psychiatric training to intensive psychoanalysis (Eysenck, 1952.) This explanation gains plausability from the fact that reported improvement rates for various series of neurotics treated by different forms of psychotherapy hover around sixty percent. (Appel, Lhamon, Myers and Harvey, 1953.) This is the same as that reported for the placebo effect in illnesses in which 'emotional components' may play a major role, such as "colds" (Diehl, 1933) and headaches (Jellinek, 1946.)

To show that a specific form of treatment produces more than a nonspecific placebo effect it must be shown that its effects are stronger, last longer, or are

qualitatively different from those produced by the administration of placebos, or that it affects different types of patients. Knowledge of all these matters is still fragmentary, and much work needs to be done.

With respect to the duration of improvement, if it could be shown that the placebo effect is of shorter duration than changes specific to a given psychotherapy, this would provide one kind of evidence favouring that theory of psychotherapy. However no detailed study of the limits of duration of the placebo effect has been made.

It would also be helpful to know if patients could be differentiated according to attributes which predisposed them to a toxic or non-toxic (or, as some writers prefer, positive or negative) placebo effect. If patients who improved with a particular form of therapy were all known to be 'positive' placebo reactors, then the improvement could not be attributed to the specific form of treatment.

The so-called placebo effect should be looked upon as an epiphenomenon of complicated psychological processes, which are far more important than the disarmingly simple means utilised for its realisation. In the light of the considerations mentioned above, it should now be clear

that the area which demands pressing attention is that encompassing the concept of the placebo reactor. We would maintain that an important solution to the problems of placebo effect in any type of clinical situation or research design, is an adequate study of the factors contributing to the response of the placebo reactor. It is with this awareness that the present study was undertaken.

THE AIMS AND RATIONALE OF THE PRESENT STUDY

From the review of the literature presented earlier, it is apparent that insufficient well-defined and conclusive work has been done in investigating the factors influencing the placebo reactor. Despite the common recognition of the frequency of placebo reactions there has been no really adequate and detailed study of the psychological aspects of the problem.

Broadly speaking, the present experiment has two main aims. Firstly, an attempt to demonstrate the existence of a placebo reaction, as elicited by the present group of experimental subjects, and to present a method of measurement of the reaction. Secondly, an attempt to find if placebo reactors as measured by the present study, present any consistent personality syndrome.

In view of these aims, and because of certain indications from previous experiments, the study contains a central hypothesis, which is: "That there are identifiable placebo reactors and identifiable non-reactors. There will be more of the former among high anxious persons, and the reactors will be further differentiated in other behaviour characteristics, e.g. they will be more suggestible generally."

This central hypothesis is, however, broken down into nine shorter hypotheses to aid the design of the experiment and the subsequent testing of the central hypothesis.

1. It was shown from a review of the major studies carried out in this field, that a great deal of variation existed in the attempts to define and measure the placebo response. The present writer accepts any reaction to an inert substance as a placebo response. That is, the definition of a placebo response is not restricted to the inhibition of a response in a clinical situation (the therapeutic efficacy of the placebo) or to the production of responses which would be expected in connection with the administration of a placebo presented as a specific drug. From this position, Hypothesis 1 may now be presented.

Hypothesis 1: That an experimental group of subjects to whom placebo is administered will show more changes in symptoms, and intensity of symptoms, than a control group to whom no placebo was administered.

This hypothesis arises, firstly, from the author's contention that if a "placebo reactor" exists, then he should react, by definition, to any type of placebo i.e. to a placebo presented as any type of drug, or a placebo merely presented as a drug, unlabelled. If the basic mechanisms of the placebo reaction are to be studied, it would seem most important to introduce as the experimental variable, one which is least contaminated by other, intervening variables, and their connotations, to allow

the subjects scope, as it were, for reaction in any direction.

Secondly, all studies reviewed measured the placebo reaction in only two ways: either by amount of therapeutic efficacy, or by the total number of responses given after the administration of placebo. In this way, not only was each study limited in its conception of what constituted a placebo reaction by the type of response demanded, but "a reactor" could only be defined in terms of the type of "drug" or situation which was presented.

In addition, the method of measuring the placebo reaction by the total number of responses given, seems particularly crude. As used by previous experimenters, no control measures were provided, so as to compare the total number of pre-placebo responses with the total number reported after the administration of placebo. However, this in itself is insufficient. For example, any individual subject may present an equal number of symptoms in the pre-placebo situation as after placebo administration. These may be entirely different symptoms, however, so that the subject should be labelled as a reactor. What is needed is a measure of change in the responses reported under the two conditions. Also, it would be maintained that a measure of the degree or intensity of symptoms is needed, as any individual subject might report no change in symptoms, but

a greater degree of intensity of symptoms after taking placebo. From this, Hypothesis II is presented.

Hypothesis II: That the measurement of the total number of symptoms reported by subjects after the administration of placebo is insufficient evidence of placebo reaction.

2. It was also shown from a review of the literature, that anxiety has often been associated with placebo reaction, either in the experimental situation itself, or with anxious subjects as such (cf. Beecher, 1955; Tibbetts and Hawkings, 1956; Lasagna 1954.) In the light of this attitude, Hypothesis III is advanced.

Hypothesis III: That those subjects with high anxiety scores will show a greater number of reactions to placebo, as defined by this study, than those with low anxiety scores.

However, an additional point must be made, at this stage. On reviewing the questionnaires used by some experimenters as their instrument of measuring placebo reaction, it was found that many of the items were similar to those contained in tests typically used to measure anxiety (for example, the Taylor Manifest Anxiety Scale, which has many items with physiological connotations.) If it is remembered that these workers, in addition, generally used as their definition of placebo reaction, the total number of symptoms reported after administration of placebo, then it

can be seen that this disregards the possibility of those subjects who are highly anxious, responding to a greater number of these symptoms, not because they are reacting to placebo, but because they are reporting responses symptomatic of their degree of anxiety. Because of this possibility, Hypothesis IV is presented.

Hypothesis IV: That those experimental subjects labelled as high anxious, will give more responses to the questionnaire used as a measuring instrument, both in the pre-placebo and the placebo conditions, than will those experimental subjects labelled as low anxious.

There has long been a general feeling that neurotics are more prone to react to placebo (cf. Sainz et al., 1957) than are non-neurotics. An attempt was made to verify this approach, by Hypothesis V.

Hypothesis V: That those experimental subjects with high neuroticism scores will show a greater number of reactions to placebo, as defined by this study, than those with low neuroticism scores.

In view of the relationships found between anxiety (as measured by the 16 PF) and neuroticism (as measured by the M.P.I.) (cf. Eysenck, 1958; Thorn, 1960) it would be expected that if Hypothesis V were confirmed, Hypothesis III would be also.

The attempts made to relate suggestibility to placebo reaction have already been outlined (see p.72), as have the

difficulties involved in measuring suggestibility. It was decided to accept Evans' finding of three main factors of suggestibility. These are, Factor A, primary suggestibility, which, as a unitary trait, was found to have factor loadings which agreed with those making up the factor Eysenck labelled as 'primary suggestibility"; Factor B, prestige authoritarianism; and Factor C, uncritical acceptivity or indirect learning. Three hypotheses were derived using these results.

Hypothesis VI: That scores obtained by the experimental subjects in the measurement of primary suggestibility (as defined by Eysenck) will be positively related to their placebo reaction, as measured by the present study.

Hypothesis VII: That scores obtained by the experimental subjects in the measurement of Evans' suggestibility Factor B, prestige authoritarianism, will be positively related to their placebo reaction, as measured by the present study.

Hypothesis VIII: That scores obtained by the experimental subjects in the measurement of Evans' suggestibility Factor C, uncritical passivity or indirect learning, will be positively related to their placebo reaction as measured by the present study.

In view of the relationship reported by Eysenck (1947) between primary suggestibility and neuroticism and anxiety, it would be expected that if Hypothesis VI were confirmed,

than Hypothesis lll and V would be also.

As Eysenck pointed out in 1961, there has been no study carried out to indicate whether placebo reactors as a group are more introverted or extraverted (as measured by the M.P.I.) Although Eysenck offered no hypothesis in relation to this, an attempt was made in the present study to investigate the possible relationship between introverts (dysthymics) and placebo reaction. Such a relationship was hypothesised because Eysenck (1947) reported a correlation between dysthymic and primary suggestibility. Later, (1960) he suggested that primary suggestibility might be related to placebo reaction.

Hypothesis IX: That those experimental subjects with low extraversion scores (as measured by the M.P.I.) will show a greater number of reactions to placebo, as defined by this study, than will those with high extraversion scores.

In summary then, this study was an attempt to investigate the following hypotheses.

1. That an experimental group of subjects to whom placebo is administered, will show more changes in symptoms than a control group to whom no placebo is administered.

2. That the measurement of the total number of symptoms reported by subjects after the administration of placebo is insufficient evidence of placebo reaction.

3. That those subjects with high anxiety scores will show a greater number of reactions to placebo, as defined by this study, than those with low anxiety scores.

4. That those experimental subjects labelled as high anxious, will give more responses to the questionnaire used as a measuring instrument, both in the pre-placebo and placebo conditions, than will those experimental subjects labelled as low anxious.

5. That those experimental subjects with high neuroticism scores will show a greater number of reactions to placebo, as defined by this study, than those with low neuroticism scores.

6. That scores obtained by the experimental subjects in the measurement of primary suggestibility (as defined by Eysenck) will be positively related to their placebo reaction, as measured by the present study.

7. That scores obtained by the experimental subjects in the measurement of Evans' suggestibility Factor B, prestige authoritarianism, will be positively related to their placebo reaction as measured by the present study.

8. That scores obtained by the experimental subjects in the measurement of Evans' suggestibility Factor C,

uncritical passivity or indirect learning, will be positively related to their placebo reaction as measured by the present study.

9. That those experimental subjects with low extraversion scores, as measured by the M.P.I., will show a greater number of reactions to placebo, as defined by this study, than will those with high extraversion scores.

An outline and rationale of the experimental design used in the investigation of these hypotheses is presented in the following section. However, basically, the experimental design allowed for two groups of subjects, one tested under conditions of placebo and no placebo for equal time intervals, and a second, control group, whose symptoms were measured under a no placebo condition. These groups were categorised according to their scores on the T.M.A.S., and were also given the M.P.I. Scores on these variables were used to test hypotheses relating to reactions to placebo and personality variables. In addition, an attempt was made to arrive at a more sensitive measure of placebo reaction than reported in previous studies.

THE EXPERIMENTAL DESIGN

1. The Choice and Use of Experimental Subjects

With the single exception of Abramson et al., (1955) all subjects used in the studies reported were hospital patients undergoing treatment, or were being administered placebo under conditions designed to bring about the alleviation of physiological or psychological symptoms. This meant that the placebo was being used in a very specific context, namely to inhibit responses, and in very specific conditions, namely those involved with 'suffering' and anxiety. It would be maintained that this approach is not conducive to providing an answer to a statement such as Eysenck's: "It is not known whether the tendency to react to placebos is a unitary trait." (Trouton and Eysenck, 1960, p.635.)

The indiscriminate use by all workers of subjects of various ages and both sexes, in the hope that an ad hoc appraisal would indicate significant differences between these variables and placebo responses seems methodologically inadequate as an approach. Rather, it would be more useful to make an informed prediction that particular variables were related to placebo response, and choose a sample accordingly.

Such studies as those reported by Jellinek (1946) and Abramson (1955) made use entirely of volunteer subjects, in spite of the warnings reported previously by, for example,

Lasagna (1954) that this could lead to sample bias (p.50).

Finally, no study reported the use of subjects to form any type of control group. This meant that no comparative measures were available, in order to test if responses given by subjects who were receiving placebo were significantly different from responses they might report under non-placebo or pre-placebo control conditions.

The following precautions were taken in the present experimental design. Firstly, only female subjects were employed, in order to prevent possible inter-sex interaction, and sex differences which could not be controlled, in relation to placebo reaction. Secondly, as many non-volunteer subjects were used as was possible. Thirdly, the use of hospital patients was avoided, and instead relatively normal and non-hospitalised subjects were used, who were taken from a relatively homogeneous undergraduate population.

In order to test Hypotheses 3, that those subjects with high anxiety scores will show a greater number of reactions to placebo, as defined by this study, than those with low anxiety scores, members of the undergraduate

population were given the Taylor Manifest Anxiety Scale, and the 16PF (which was scored for the second order factor of Anxiety, U.I.(L) and (Q) II). A sample from these subjects was grouped arbitrarily into categories of high and low anxious subjects on the basis of their scores on the T.M.A.S. The remaining subjects formed a medium anxious group. This procedure was used merely to demarcate groups of anxious subjects in order to aid the testing of Hypothesis III.

In order to test Hypothesis 5 and 9, adequate variance was ensured on the personality variables of neuroticism and extraversion. The variables were defined and measured by the M.P.I.

Finally, a second undergraduate population was given the T.M.A.S., and a group of women students were matched with the experimental group on the basis of their scores. This served as a control group. The rationale and use of control measures will be elaborated in a later section.

2. The Selection and Use of the Experimental Situation

Beecher asserted in his study (1955) that a stressful situation is necessary for placebo reaction to occur. However it would seem necessary to separate reaction to a distressing situation per se, and reaction to a placebo which was thought to be an analgesic. It is difficult to generalise from the use of subjects in a hospital situation, to the population at large. How do people react, for example, when, as relatively normal healthy individuals they are confronted with the prospect of taking a placebo which is presented as an active drug?

The Abramson study (1955) was designed to answer this question, but the subjects were informed that the drug they were receiving was LSD-25, and this tended to introduce significant cues into the situation. In addition, the subjects were not separated, but tested in groups, so that those on tap-water placebo were able to observe those on actual LSD-25 (albeit unknowingly.)

Such an approach would appear to limit the advantages of using non-hospitalised subjects, and also the chance of assessing the relationship of suggestibility to placebo response.

In 1959 Orne presented a paper to the A.P.A. on the demand characteristics of an experimental design, and their implications. His theme has a great deal of relevance, both for criticisms advanced about previous work in the field of placebo reaction, and for any proposed experiment to be presented. Orne stated,

> "We conceive of the experimental situation as one kind of social situation in which the roles played by the subject and experimenter are accompanied by specific and predictable attitudes and motives. It is these attitudes and motives which may give rise to a systematic experimental effect which should be at least considered if not controlled." (Orne, 1959, p.1).

These 'systematic experimental effects' were denoted as demand characteristics.

He went on to assert that the volunteer subject is highly motivated to behave in accordance with what he believes is the experimenter's hypothesis. It is therefore of the utmost importance that the minimum number of cues is presented knowingly or unknowingly to the subject in the experimental situation. It is obvious that any

perception of cues by a subject being administered placebo will have a profound effect upon any results obtained. Therefore, using active drugs in conjunction with placebo, in a situation where subjects are able to gain multitudinous cues as to the type of reaction expected does not seem a valid approach to the measurement of a placebo response per se. Too many obviously intervening variables are able to confound the reaction. When a subject will utilise whatever cues are available in order to formulate his own ideas of what the purpose of the experiment is, then these cues must be kept to a minimum. It is, of course recognised that there is often a specific need for subjects to become aware of certain cues as part of the experimental design, e.g. when telling subjects a placebo is a specific type of drug.

In the present study the experimental situation was kept as unstructured as possible by informing the subjects participating that they were administered a drug which must remain unnamed, for in any valid drug study the active agent must remain unidentified in order to prevent imaginary reactions to it

because of preconceived notions about it, or previously acquired knowledge.

Also, each subject was administered the "drug" in individual sessions, so as to avoid a group interaction situation. The situation was that of a University Department, not a hospital ward, and each subject was therefore given the impression of an experimental situation, in situ, without any hospital connotations.

It must be understood that the experimenter is not the ideally impassive, objective observer that we often pretend he is. In particular many would feel that the sex and/or personality of the experimenter can have particular effect in the experimental situation (cf. Eysenck, 1943; Stukát, 1958; Evans, 1962.) However, Abramson (1955), Beecher (1953), Lasagna (1954) and Wolf (1957), all used a team of male experimenters who interacted in the experimental situation with a sample comprising both sexes. In order to avoid the complications which could arise from duplicating this condition, use was made of only female subjects, who were supervised at all times by the same (female) experimenter.

Every study reviewed also made use of an active drug in its experimental rationale. No necessity is seen for this approach. The essence of the situation appears to be that the subject believe an active agent is being administered, whatever the explanations given. To make

use only of placebo dismisses many problems, such as cues from the effects of active drugs being used concurrently with placebo, and it facilitates the measurement of a 'pure' placebo response in that there are no 'interfering' reactions from a drug to be considered. In this study, the placebo served as the experimental variable, rather than the control to the experimental drug, as is usual. It was proposed, therefore, to administer placebo to all subjects, under the guise of an active drug. All subjects were told they were participating in an experiment to study the physiological and psychological effects of a drug, still in the experimental stage, which must remain unnamed, and uncategorised (i.e. it was not even indicated that the 'drug' was a stimulant or depressant.) This approach allowed for adequate 'scope' of response from potential reactors. They were not specifically asked to inhibit a symptom (response) as in the experiments produced by Wolf et al., (1957); Jellinek, (1946); Gliedman et al., (1958); or to produce a response (cf. Abramson et al., 1955.)

These specified experimental conditions were seen as necessary control measures for the testing of the two broad aims of the experiment listed earlier. These were, to demonstrate the existence of a placebo reaction as elicited by the present group of experimental subjects, and to

present a method of measuring the reaction; and to find if placebo reactors, as measured by the present study, presented any consistent personality syndrome. From these aims rose the nine hypotheses listed.

Finally, an attempt was made to keep the demand characteristics of the experimental situation to a minimum. This was checked and verified by means of a post-experimental demand characteristics interview along lines suggested by Orne (1959) and which is designed to determine how subjects perceive the experiment in which they are participating in terms of its purpose and the experimenter's hypothesis.

3. The Choice and Use of a Questionnaire to Measure Placebo Reaction.

Although the disadvantages of the questionnaire method in research (e.g. lack of validity, and unreliability) are recognised, the use of a questionnaire to measure placebo reaction in this study was thought to be the only method feasible. Subjects often have great difficulty in verbalising their own reactions, especially as far as mood changes are concerned, and a questionnaire rating can help overcome this. It is obviously also inconvenient for both subjects and experimenter to spend many hours in each other's company recording reactions, when the subjects can note the degree and time of reaction by questionnaire without close supervision. For these and allied reasons, most workers

in the field have resorted to the use of questionnaires as measuring instruments.

The questionnaire used in the present study provided for four methods of measurement of the placebo response.

i. The frequency of response
ii. The change of response
iii. The degree or amplitude of response
iv. The latency of response

This was done by using a questionnaire made up of a number of symptoms. Attached to each item in the questionnaire was a rating scale which allowed the subject to rate how affected by the symptom she was. In addition, a time scale, listing a number of possible time intervals, enabled the subject to indicate at what time interval (this only after administration of placebo) a particular symptom occurred. The use of a rating scale attached to each item so that subjects could report the degree to which they were affected by a symptom was similar to methods used by Beecher (1959) and Gliedman et al., (1958.) In the present study, the subjects were able to rate for degree of affect of each symptom in the following manner:

Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

The change of response was measured by taking the change in frequency or degree of response to individual items for any one occasion, and comparing it with the frequency or degree of response shown for the same items on a different occasion.

The measurement of the mean number of symptom responses for each subject involves some difficulties in the choice of items making up the questionnaire. This is because the majority of subjects would be guided by the categories encompassed by the questionnaire. An attempt was made to cope with this situation in three ways. Firstly, by instructing subjects to report any symptoms which they exhibited which were not on the questionnaire. Secondly, by informing them that symptoms could occur which were not listed, because the effects of the 'drug' were not familiar enough to enable a complete coverage of all possibilities. Thirdly, by using as the basis of the questionnaire all those questions which received the greatest frequency of answers as reported by various other studies. In this way, a list of questions purporting to measure a variety of symptoms was compiled, using data provided by Frank (personal communication, 1961, from work completed, 1959); Abramson et al., (1955) and Beecher (1959), as well as the inclusion of some items purely by personal judgement.

It was hoped that the use of items from questionnaires used by a number of workers would allow a comparitive study of frequencies of response to items to be made, and it was carried out as an observation which was made to contribute to the understanding and testing of Hypothesis II.

4. The Choice and Use of Methods of Control

It was thought necessary in the present study to obtain pre-placebo responses to the symptom questionnaire. That is, to check the possibility of there being a significant difference between the number of responses, or the type of responses, or the reported intensity of responses, produced under placebo, and the number, type, and intensity of possible responses producable under non-placebo conditions, i.e. of symptoms reported without drugs or placebos.

Accordingly, two main types of control were used in this study. Each experimental subject was issued with a questionnaire over a pre-study time period equivalent to that during which placebo was taken. The questionnaires were identical with those measuring reaction to placebo.

The major disadvantage of this approach is that any knowledge of the control purpose of the questionnaire on the subjects' part could well bias subsequent results. In order to avoid this situation, subjects were given an unlabelled questionnaire and told to fill it in as instructed, all before it was disclosed that the object of the experiment was to test an 'active drug.' In other words, the experimental subjects completed the questionnaire in ignorance of the purpose of the experiment.

The second major control method was the use of a control group, matched with the experimental group on the personality variable of anxiety, as measured by the T.M.A.S. This group of subjects, also in ignorance of the purpose of the experiment, merely filled in the questionnaire used to measure placebo reaction for a time period equivalent to that during which the experimental group answered the questionnaire under the two conditions of pre-placebo and placebo. This enabled a comparison to be made between the responses given by the experimental group, which received the experimental variable, placebo, at a certain stage in the study, and a control group which responded over an equivalent time period without the introduction of the experimental variable.

It has already been stated that an additional method of control was to keep the subjects ignorant of the 'type'

of drug being used in the study, in order to prevent situational cues affecting the type of placebo reaction obtained. The proposition was advanced that if a placebo reactor existed as a consistently reacting individual, then he should report being affected by the administration of any type of 'drug,' or even a placebo merely introduced as an unspecified drug.

A final method of control was to keep the experimenter in ignorance of the anxiety group to which each subject had been allocated. This was in order to eliminate experimenter bias in the experimental situation arising out of such knowledge, and perhaps using it unconsciously or consciously to further the success of testing Hypotheses 3 and 4.

5. The Selection and Use of the Tests of Suggestibility

Some of the problems involved in the use of suggestibility tests to establish a relationship between suggestibility and placebo reaction have already been outlined (see p.72.)

There it was pointed out that Gliedman et al., (1958) were the only investigators who actually put to the test the widely held theory that placebo reactors were suggestible. They used the Body Sway test as a measure of primary suggestibility. However, it is difficult to draw conclusions about the relationship of suggestibility to placebo reaction, from this study

because the measure of 'placebo reaction' allowed for no comparative control study. In addition, the Body Sway test was administered by five different experimenters, despite some evidence that this can affect subjects' responses (Eysenck, 1943.)

It was mentioned that Evans (1961), in a re-factorisation of Eysenck's original data (1945) confirmed his factor of Primary Suggestibility. But he found "no basis for identifying any of the remaining factors with the concept of 'secondary suggestibility' defined by Eysenck (1947.)" (Evans, 1961, p.9.)

Eysenck and Furneaux (1945) assumed that there were two orthogonal factors in their complete matrix, and this assumption was made to justify the subdivision of the matrix. The subdivided matrix was factored to establish the tenability of the two assumed factors. Evans quite justifiably pointed out that, apart from the circularity of the argument, these assumptions were unwarranted unless it was assumed that the residual correlations after the extraction of these factors were insignificant. He concluded, "The claim that there are only two independent factors in the whole matrix is invalid ..... It is also noted that some of the correlations ignored by the

subdivision of the matrix are as large as some of the correlations between the tests of 'secondary suggestibility'." (Evans, 1961, p.6.)

Four factors were extracted by a Thurstone centroid factor analysis, and rotated graphically to simple structure. "With the exception of factors A and B, whose hyperplanes were negatively correlated (r=-.34) the factors are orthogonal." (Evans, 1961, p.7.)

While Evans' 'Factor A' agreed with Eysenck's concept of Primary Suggestibility, 'Factor B' saturated significantly only three of the six tests of so-called 'secondary suggestibility.' A 'subtle, prestige', interpretation of the factor, as presented by Eysenck (1945) was not supported by the data. Evans claimed, "but rather [it] is a mixture of command authority blended with prestige." (Evans, 1961, p.10.)

This is particularly convincing in view of the fact that all test variables loading on the factor had an aura of authoritative statement of fact, or command. For example, in descriptions of the tests reported by Eysenck and Furneaux, the subject was "told that they all differed in weight," "told that his sense of smell was to be tested," (p.487-488, italics added.)

A third factor, labelled 'Factor C' by Evans, was saturated most significantly by the Heat Illusion test.

Eysenck (1947), Furneaux (1948) and Weitzenhoffer (1953) have implied that the Heat Illusion test may belong to a third factor, although they would probably argue that it was not independent of the other factors.

Evans' interpretation of the factor was as follows, ".... it may be reasonable to postulate a sort of indirection, or uncritical acceptivity of the implied situation by the suggestee as the basis of the factor." (Evans, p.11, 1961.)

Thus, from this study, it can be seen that a much more subtle approach to the concept of suggestibility is made possible. 'Secondary suggestibility' was found to be not a unitary trait, but two factors, one encompassing the concept of authoritarianism, demanding prestige, the other to be interpreted in terms of "uncritical acceptivity" or "indirect learning."

Because of the wide range of views held by theorists in the field of placebo research, as to the 'type' of suggestibility involved in placebo reaction i.e. whether it was a function of the situation, or inherent attributes of the patient, or both, the work of Evans provides an excellent opportunity for a more sensitive appraisal of the problem. Hypotheses 6, 7, and 8, as listed previously, were therefore an attempt to evaluate the relationship of each of Evans' three main factors of suggestibility

(Factor A, primary suggestibility; Factor B, prestige authoritarianism; Factor C, uncritical acceptivity or indirect learning) to any reaction to placebo displayed in our study.

The choice of tests of suggestibility to measure these factors was contingent upon the data reported by Evans which is presented below, in Table VI.

TABLE VI. Rotated Centroid Factor Solution of 12 Tests of Suggestibility, reported by Evans (1961.)

	Eysenck & Furneaux (1945) Factors from sub-divided matrix		Evans' re-factorisation of complete matrix				Communalities, Evans' re-factorisation	
Test	P	S	A	B	C	D	h^2est.	h^2obt.
1. Hypnosis	80		94	32	36	-07	73	1.01
2. Post hypnotic	77		85	48	05	00	72	75
3. Pendulum	64		75	56	-25	-03	75	71
4. Body Sway	92		92	-34	-32	-11	75	97
5. Press	38		27	-04	-01	56	47	42
6. Release	73		62	-05	07	33	64	64
7. Heat Illusion		25	20	10	76	02	51	62
8. Picture		27	-07	08	41	27	31	26
9. Ink blot		71	05	48	29	-02	48	47
10. Odours		62	07	61	10	-08	38	46
11. Weights, Imp.		06	04	29	-23	11	27	15
12. Weights, Pers.		43	-15	49	-18	33	48	49
Contribution to total variance	55%	20%		42%	10%	6%		58%

Note: Factor Loadings >.20 underlined > .40 double underlined

The tests included were those with a sufficiently high loading on each of the first three factors to obtain an adequate measure of the factor. To this end, the Body Sway test was chosen, with a loading of .92 on Factor A; the Ink Blot test, with a loading of .48 on Factor B; and the Heat Illusion test, with a loading of .76 on Factor C. In addition, the Arm Bending test (passive) was included, because of previous work (Thorn, 1960) which indicated that the test loaded .66 on a Factor of suggestibility on which the Body Sway test loaded .80. This test was therefore used as an additional measure of primary suggestibility.

It is recognised that the study by Evans conflicts with one of the major contributions to the theory of suggestibility, and it might be questioned that the tests of suggestibility being used were chosen on the basis of his work. However, the precaution was taken of also choosing tests which loaded on Eysenck's alleged factor of 'secondary suggestibility'. This does not indicate, however, a completely eclectic position. The writer is specifically interested in applying the more subtle concepts of suggestibility, as supplied by Evans' work, to placebo reaction.

Because keeping the purpose of the present experiment from the subjects involved was considered of vital importance,

all tests of suggestibility were administered after the series of placebo had been given, in order that no cues might be attached to the situation.

6. The Choice and Use of Time Intervals in which to Study Placebo Reaction

Early reports of placebo reaction (cf. Jellinek, 1946) were more concerned with the study of the response per se, rather than the influence upon it of such variables as time intervals. Many experimenters neglected either to state the time interval over which placebo had been administered, or to report such time periods accurately.

Lasagna's work (1954, 1958) was possibly the first to indicate that the number of 'doses' of placebo had significance. However nowhere was a statement made of the time intervals between the respective dosages. He reported a general decrease in the effectiveness of placebo (i.e. in effective response to it) of from 53 percent effectiveness for one dose per patient to 15 percent effectiveness for four or more doses per patient, (1954.) However a decrease in effectiveness is not necessarily the equivalent to a decrease in total placebo response.

In 1957, Wolf et al., reported, "It was not possible on the basis of 1, 2, 3, 4, 5 or 6 tests to predict whether

or not an individual would display a placebo response on subsequent testing." (Wolf et al., 1957, p.840.) These were discouraging results indeed, pointing to no consistency of placebo reaction, over successive administrations greater than would be expected to occur by chance. However these results are at variance with all other reports in the literature, and we have already discussed possible weaknesses in the experiment which could account for these results (see p.39.) This is one of the problems under investigation in the present study, encompassed by Hypothesis 1.

Rosenthal et al., (1956) approached the problem with a conviction that ".....the placebo effect ... can ... be enduring." (p.296.) They quoted an experiment in which they administered either mephenesin or placebo over four two-week periods. The greatest decrease in distress following placebos was felt during the first two-week trial period. After that, a slight but statistically insignificant rise in distress occurred, and, at the end of eight weeks, the placebo effect was about as great as after two weeks. They add, "Unfortunately, our data yielded no information on how much longer it might have endured." (Rosenthal et al., 1956, p.297.)

Disagreement as to consistency of reaction could be based upon the time intervals over which placebo was given.

Lasagna et al., (1954) for example, found only 14 percent of their patients were consistent reactors i.e. showed the effect with every placebo dose (which apparently varied, the largest number being reported as "4 or more"); and 31 percent were consistent non-reactors, while 55 percent showed the effect on some occasions but not on others. This contrasts with the findings of Jellinek (1946) whose patients with headaches were, for the most part, either in the always-relieved group or the never-relieved group, with only a small percentage of patients showing inconsistency of response. Differing time intervals of study, unreported, by Jellinek, and varied, by Lasagna et al., could account for this. However, as Rosenthal et al., point out, the apparent contradiction in findings could also result from the difference in the cause of the pain in the two series, or from other factors. In any case it indicates that the problem is a complex one needing more study.

It is preferred at this point, to follow the indications of work carried out by Glaser et al., 1953. As with the present study, placebos were administered in one of a series of experiments, without any accompanying active agents, and the subjects were given questionnaires on which to report the symptoms which appeared, "repeatedly at intervals of 2-5 days, and the incidence of symptoms

decreased by about 20 percent until the third test, after which it remained at a steady level even if different dummy tablets were given in turn." (Glaser et al., 1953, p.43.)

Accepting tentatively the indications from this study, placebo was administered to the experimental subjects once a day for four consecutive days, and the questionnaires were administered to the same subjects without placebo, for an equivalent time period. The control group of subjects completed the questionnaire once a day for 8 days. If Glaser's observations are valid, then a four day testing period for each condition would seem sufficient in order to assess consistency of reaction.

7. The Choice and Use of the Personality Tests

Only two of the many reports making use of personality measures, Abramson et al., (1955) and Lasagna et al., (1954) used tests other than interview techniques of clinical diagnosis and projective tests. In both cases the sub-tests of the Wechsler-Bellevue were used to gain some clinical picture of the subjects' attributes and personality structure. Any attempt to estimate the personality traits of placebo reactors has been handicapped by lack of use of valid and reliable measures. To this end, tests were selected in this study which were

considered to be the most adequate measuring instruments available of the personality variables entailed in Hypotheses 3, 4, 5 and 9.

A. The Measurement of Anxiety

Two of the Hypotheses entail a measure of the personality variable of anxiety. Hypothesis 3 states: That those subjects with high anxiety scores will show a greater number of reactions to placebo, as defined by this study, than those with low anxiety scores. Hypothesis 4 states: That those experimental subjects labelled as high anxious, will give more responses to the questionnaire used as a measuring instrument, both in the pre-placebo and placebo conditions, than will those experimental subjects labelled as low anxious.

Anxiety has been measured in a variety of ways, but there is a lack of general theoretical agreement among measures. This is perhaps due to the methodological problems, involved in measuring 'anxiety.' The problems encountered in measuring clinical anxiety are primarily those of definition and reliability of measurement.

Because the term "anxiety" has a variety of behavioural referents, the operational definition should be explicit, and the behaviours labelled "anxious" should be specified.

On surveying the tests available, the Taylor Manifest Anxiety Scale was chosen as a criterion measure for selection of subjects. Evidence that the T.M.A.S. is not a very stable measure under certain conditions, evidence that it does not have much in common with certain other measures of anxiety, and evidence that it is derived from items that may be said to define certain other traits, has been tendered and accepted or rejected in fierce debate by many writers. Much contradictory evidence is available.

Taylor wrote of criticisms of the test,

> "The construction of the test was not aimed at developing a clinically useful test which would diagnose anxiety, but rather was designed solely to select subjects differing in general drive level. Thus the question of the scales' "validity" (i.e. its agreement with clinical judgements) is in a sense irrelevant to the experimental purposes for which the test was developed. In light of this, the test might better have been given a more noncommittal label, such as a measure of emotionality, although the fact that the items on the scale were selected by clinicians as referring to manifest anxiety as it is described psychiatrically does not make the title completely inappropriate nor a relationship between clinical judgements and M.A.S. scores unexpected. Certainly the generality of the experimental findings with the M.A.S. would be increased if correlations were found with other definitions ..... However, regardless of the results of such studies, it should be clearly understood that "manifest anxiety" has been defined operationally only in terms of test scores...." (Taylor, 1956, pp.303-304.)

However, it was a decision of this study to accept the T.M.A.S. as an operational definition of 'anxiety', despite the problems attached. In addition, an attempt was made, as Taylor suggested, to find correlations of the test with other definitions of anxiety. This was carried out as an incidental observation, which was made as a contribution to understanding the phenomenon in question and not the testing of Hypotheses 3 and 4. Specifically, use was made of Cattell's second order factor U.I. (2) and (Q) II: Anxiety Vs Integration derived from the 16PF questionnaire. Many workers in this field would accept Cattell's measure of anxiety as a more valid one. No study in the literature has reported an attempt to correlate results on the Cattell second order factor of anxiety with those on the T.M.A.S. It was recognised that differing concepts of anxiety might be involved, but it was hypothesised that a positive correlation existed between the two for the following reasons.

Both Cattell (1957) and Scheier (1957) claimed that the factor U.I. (2) and (Q) II correlated with the Objective Test factor U.I. (T) 24 (Anxiety) but not with U.I. (T) 23 (Neuroticism). However, Eysenck (1958) correlated Cattell's second order factor of Extraversion - Introversion and Anxiety Vs Integration

with his own two questionnaire factors of Introversion - Extraversion and Neuroticism, and "the resulting correlations were positive, high, and highly significant." (Eysenck, 1958, p.351.) Elsewhere, Eysenck, (1959, p.4) reports a correlation of ·34 between the M.P.I. Neuroticism and 16PF Anxiety factors (Form A) on a sample of one hundred and thirty four neurotics. The writer, in 1960, because of this and related evidence, hypothesised that a factor analysis of the variables purported by Eysenck and Cattell to measure introversion - extraversion, anxiety, and neuroticism, would in fact yield only two factors, one of neuroticism and one of introversion - extraversion. This seemed particularly plausible in the light of Cattell's description of the anxious person who scored positively on the "anxiety" pole as being miserable, submissive, timid and frightened, unstable and generally 'maladjusted,' which appeared more a description of neurosis than anxiety. The hypothesis was verified, the 16PF second order factor of Anxiety loading ·89 on a general factor of Neuroticism. This is in accordance with Eysenck's results, but contrary to the opinion expressed by Cattell in 1957.

In 1957 Bendig reported a high correlation of ·77 between the T.M.A.S. and Neuroticism as measured by the Maudsley Personality Inventory. Bendig also found the

T.M.A.S. related, but to a lesser extent, to Introversion (from the M.P.I.) He followed Eysenck in concluding that anxiety is neurotic introversion and that a good measure of it should be correlated equally with both traits. Cattell, however, brought together results from seven different factor analyses to show that Neuroticism and Anxiety were distinct factors (1957.)

Despite this, in view of the evidence reported, it would be maintained that a high correlation would be found between the T.M.A.S. and the 16PF second-order Anxiety factor, because of their mutual correlation with the M.P.I. factor of Neuroticism. By calculating such a correlation it was hoped not only to add to the general knowledge of correlates of the T.M.A.S., but to revoke the criticism of those who might support the use of the 16PF second order factor of anxiety as the selection criterion, rather than the T.M.A.S. A lack of significant relationship between the T.M.A.S. and U.I. (L) and (Q) II would be then the only justification in selecting one test in preference to the other as a measure of anxiety.

In order to test Hypotheses 3 and 4, the experimental design included the following. The T.M.A.S. was administered to a sample of subjects, and, on the basis of the distribution of scores on the test, two groups

of subjects were arbitrarily demarcated: a group with high scores on the T.M.A.S., and a group with low scores. Such demarcation of the anxious subjects in this manner was merely to enable a more precise handling of the data in order to test Hypotheses 3 and 4.

In order to study the incidental observation that 16PF second order anxiety was correlated with the T.M.A.S., all experimental subjects also completed the 16PF, and their scores were correlated with their T.M.A.S. results.

B. The Measurement of Extraversion

In order to test Hypothesis 9, that those experimental subjects with low extraversion scores, as measured by the M.P.I., will show a greater number of placebo reactions, as defined by this study, than will those with high extraversion scores, use was made of the Maudsley Personality Inventory extraversion scale.

C. The Measurement of Neuroticism

In order to test Hypothesis 5, that those experimental subjects with high neuroticism scores will show a greater number of reactions to placebo, as

defined by this study, than those with low neuroticism scores, the M.P.I. neuroticism scale was used. There would seem sufficient empirical evidence to justify this choice (Eysenck, 1959).

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SECTION II

1. THE SELECTION OF SUBJECTS

The Sex of the Subjects

Only Gliedman et al., (1958) reported any sex differences in frequency of reaction to placebo. This was a slight difference in favour of female subjects. However, the majority of studies showed no agreement with this.

Beecher claimed (1952) that women prove more difficult as subjects in experiments in this area, because sex characteristics can interact with other variables in the experimental situation. However, with adequate control measures, the present writer sees many of these problems as diminishing in importance.

Women were chosen as subjects in the present experiment in order to eliminate the possibility of uncontrolled effects from the interaction of a female experimenter with male subjects. Using subjects of the same sex also provides a control for possible interaction between personality variables attributed to sex differences, and reaction to placebo.

Beecher's note of caution is, of course, justified. When the physiological and psychological effects of the

placebo (presented as a drug) are to be studied, there obviously cannot be an overlap between these responses, and factors such as the physiological and emotional concomitants of menstruation. For this reason, no female subject was used in this investigation who was menstruating at the time of filling in either the questionnaires administered pre-placebo, or the questionnaires completed while on placebo. In addition, no subject was used while undergoing any violent emotional upheaval or physiological disability. This was determined by interview. These conditions also applied to the subjects used in the control group.

Approximately eighty women undergraduates were administered the Taylor Manifest Anxiety Scale, (T.M.A.S.) and the Maudsley Personality Inventory, (M.P.I.). As this sample of undergraduate women was unlikely to be representative of the female population, it was decided to correct this as much as possible in the selection of the final experimental group. Of the subjects able to participate in the main experiment, a sample of forty-five was selected, with reasonably normal distributions of scores on the personality variables of anxiety, neuroticism and extraversion, and with the

means and standard deviations as close as possible to the means and standard deviations for the general norming population. Unfortunately, although Eysenck provides these figures for the M.P.I. scales, no comparable figures were available for the T.M.A.S. Thus, in the case of the T.M.A.S. scores, the mean and standard deviation were made consistent with those of the original sample of eighty female A.N.U. undergraduates.

TABLE 7: A comparison of the present experimental group means and standard deviations with sample norms provided by Eysenck (1959, N = 1800) for M.P.I. Neuroticism and Extraversion scores, and means and standard deviations for the original sample of subjects and the experimental group selected from it for their scores on the T.M.A.S.

Personality Variable	Experimental Group		Norming Population		F Test		t Test		χ^2 Test of goodness of fit to normal curve	
	$\bar{X}$	S.D.	$\bar{X}$	S.D.	F	p	t	p	χ^2	p
Extraversion	26.96	9.34	24.91	9.71	1.08	.05	1.08	.05	12.09	.10
Neuroticism	21.71	11.88	19.89	11.02	1.11	.05	1.01	.10	5.36	.60
Anxiety	16.52	9.47	16.90	8.92	1.13	.05	1.84	.05	6.33	.05

In order to facilitate the testing of Hypothesis IV, that those experimental subjects labelled as high anxious, will have more responses to the questionnaire used as a measuring instrument, both in the pre-placebo and placebo conditions, than will those subjects labelled as low anxious, the experimental subjects with scores of 22+ on the T.M.A.S. were arbitrarily labelled as high anxious, and those with scores of 11- were labelled as low anxious.

The Selection of the Control Group of Subjects

Approximately sixty women undergraduates were given the T.M.A.S. From these, twenty-four were selected. The mean score for this group, called the control group, matched that of the experimental group as closely as possible. The comparative scores may be seen in Table 8.

TABLE 8: A Comparison of the Means and Standard Deviations of the T.M.A.S. scores of the 45 experimental subjects and the 24 control subjects.

	$\bar{X}$	S.D.
Experimental	16.52	9.47
Control	16.58	9.08

None of the subjects used in the experimental group were used in the control group, and the two groups were selected from different samples of subjects.

The control group filled in the questionnaire used to measure reaction to placebo for eight days, as did the experimental group. Similarly, an average gap of three weeks was left between the filling in of the first set of four questionnaires and the last set.

It was thought necessary to set up a control group, since changes from a first to a second measure might occur in the experimental group because of practice effect or because of some other variable beyond the control of the investigator. In setting up a control group, the members of which were measured and then remeasured, at chronological times corresponding as closely as possible to those of the experimental group, it was presumed that all uncontrollable effects would be operating similarly on both groups, so that any difference in change for the two groups would have resulted from the administration of placebo to the members of the experimental group.

Matching on extraversion and neuroticism was not imperative as these variables had been found relatively unimportant as far as reaction to placebo was concerned.

TABLE 9: THE QUESTIONNAIRE

This was administered to all subjects on placebo for four days, and, without the time scale, as a pre-placebo control measure for four days.

NAME:

DATE:

INSTRUCTIONS

Listed below are a number of symptoms or problems that people sometimes have. Directly under each symptom or problem is a scale showing how affected or distressed a person may feel as a result of having the particular symptom. Please read each of them carefully and decide whether you have had the symptom since taking the drug capsule you were given today.

If you have not had the symptom since taking the drug capsule you were given today, place an X in the parenthesis above the statement "Have not had this symptom" on the scale. If you have had the symptom one or more times since taking the drug capsule you were given today, then decide whether the symptom was slightly, moderately or severely distressing, and place an X in the parenthesis above the statement which most nearly describes the amount of distress, worry or suffering you experienced. SINCE THE SAME STATEMENT IS NOT IN THE SAME PLACE ON EACH SCALE, PLEASE READ EACH ONE CAREFULLY.

In addition you are asked to indicate at what time (approximately) you noticed these effects or symptoms occurred, after having taken the drug capsule. Place an X in the parenthesis next to the time period which is relevant for you.

Example: If you are severely distressed by a headache half an hour after having taken the drug capsule, then in completing the scale number 1 regarding headaches, you would place an X over the statement "severely distressed", and an X next to the statement "half an hour", as indicated below.

TABLE 9 (continued)

1. Headaches

( )	( )	( )	(X)
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately) after administration of the drug?

( ) 10 minutes	(X) half an hour	( ) an hour
( ) 3 hours	( ) 6 hours	( ) 12 hours

If you have been slightly distressed by pains in the heart or chest, then in completing scale number 2 you would enter an X in the parenthesis ( ) over "slightly distressed", as indicated below, and if these pains were noticed three hours after having taken the drug capsule, you would enter an X in the parenthesis ( ) next to "3 hours" as seen below.

2. Pains in the heart or chest

( )	( )	(X)	( )
Severely distressed	Moderately distressed	Slightly distressed	Have not had this symptom

At what time was this noticed (approximately) after administration of the drug?

( ) 10 minutes	( ) half an hour	( ) an hour
(X) 3 hours	( ) 6 hours	( ) 12 hours

Do not spend much time on any one question. Before you hand in your completed questionnaire, please check to see that you have answered every question.

TABLE 9 (continued)

Since taking the drug capsule you were given today, how much have you been distressed, troubled, annoyed, worried, pained etc. by each of the following symptoms, and at what time?

1. Headaches

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

2. Pains in the heart or chest

( )	( )	( )	( )
Severely distressed	Moderately distressed	Slightly distressed	Have not had this symptom

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

3. Heart pounding or racing

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

TABLE 9 (continued)

4. Trouble getting your breath

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

5. Constipation

( )	( )	( )	( )
Severely distressed	Moderately distressed	Slightly distressed	Have not had this symptom

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

6. Nausea or upset stomach

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

7. Loose bowel movements

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

TABLE 9 (continued)

8. Twitching of the face or body

( )	( )	( )	( )
Severely distressed	Moderately distressed	Slightly distressed	Have not had this symptom

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

9. Faintness or dizziness

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

10. Hot or cold spells

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At What time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

11. Itching or hives

( )	( )	( )	( )
Severely distressed	Moderately distressed	Slightly distressed	Have not had this symptom

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

TABLE 9 (continued)

12. Frequent Urination

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

13. Pains in the lower part of your back

( )	( )	( )	( )
Severely distressed	Moderately distressed	Slightly distressed	Have not had this symptom

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

14. Difficulty in swallowing

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

15. Skin eruptions or rashes

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was thos noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

TABLE 9 (continued)

16. Soreness of your muscles

( )	( )	( )	( )
Severely distressed	Moderately distressed	Slightly distressed	Have not had this symptom

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

17. Nervousness and shakiness under pressure

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

18. Difficulty in falling asleep or staying asleep

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

19. Moistness of your palms

( )	( )	( )	( )
Severely distressed	Moderately distressed	Slightly distressed	Have not had this symptom

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

TABLE 9 (continued)

20. Increased appetite

( )	( )	( )	( )
Greatly increased	Moderately increased	Slightly increased	Not at all increased

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

21. Drowsiness or fatigue

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

22. Difficulty in focusing your eyes

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

23. Ringing or buzzing in your eardrums

( )	( )	( )	( )
Severely distressed	Moderately distressed	Slightly distressed	Have not had this symptom

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

TABLE 9 (continued)

24. Increased thirst

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

25. More than usually relaxed

( )	( )	( )	( )
Not relaxed	Slightly relaxed	Moderately relaxed	Very much relaxed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

26. Sensation of heaviness in your head or limbs

( )	( )	( )	( )
Severely distressed	Moderately distressed	Slightly distressed	Have not had this symptom

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

27. Feeling a warm glow

( )	( )	( )	( )
Have not had this symptom	Slightly felt	Moderately felt	Severely felt

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

TABLE 9 (continued)

28. Bad dreams

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

29. Feeling blue

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

30. Being easily moved to tears

( )	( )	( )	( )
Severely distressed	Moderately distressed	Slightly distressed	Have not had this symptom

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

31. An uncontrollable need to repeat the same actions e.g. counting, touching etc.

( )	( )	( )	( )
Severely distressed	Moderately distressed	Slightly distressed	Have not had this symptom

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

TABLE 9 (continued)

32. Unusual fears

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

33. Objectionable thoughts or impulses which keep pushing themselves into your mind

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

34. Your "feelings" being easily hurt

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

35. Feeling that people were watching or talking about you

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

TABLE 9 (continued)

36. Generally preferring to be alone

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

37. Feeling lonely

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

38. Feeling compelled to ask others what you should do.

( )	( )	( )	( )
Severely distressed	Moderately distressed	Slightly distressed	Have not had this symptom

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

39. Feeling easily annoyed or irritated

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

TABLE 9 (continued)

40. Severe temper outbursts

( )	( )	( )	( )
Severely distressed	Moderately distressed	Slightly distressed	Have not had this symptom

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

41. Feeling critical of others

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

42. Frequently took alchohol or medicine to make you feel better

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

43. Difficulty in speaking when you were excited

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

TABLE 9 (continued)

44. Feeling unaccountably nervous

( )	( )	( )	( )
Severely distressed	Moderately distressed	Slightly distressed	Have not had this symptom

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

45. Feeling your mind was slow and sluggish

( )	( )	( )	( )
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

46. Feeling indifference or lack of concern

( )	( )	( )	( )
Severely distressed	Moderately distressed	Slightly distressed	Have not had this symptom

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

47. Feeling rested and contented

( )	( )	( )	( )
Have not had this symptom	Slightly felt	Moderately felt	Greatly felt

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

TABLE 9 (continued)

48. Feeling enthusiastic and interested

( )	( )	( )	( )
Have not had this symptom	Slightly felt	Moderately felt	Greatly felt

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

49. Feeling cooperative

( )	( )	( )	( )
Have not had this symptom	Slightly felt	Moderately felt	Greatly felt

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

50. A sense of restlessness

( )	( )	( )	( )
Severely distressed	Moderately distressed	Slightly distressed	Have not had this symptom

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

51. Feeling confused and unreal

( )	( )	( )	( )
Severely distressed	Moderately distressed	Slightly distressed	Have not had this symptom

At what time was this noticed (approximately), after administration of the drug?

( )10 minutes ( ) half an hour ( ) an hour.
( ) 3 hours ( ) 6 hours ( ) 12 hours

TABLE 9 (continued)

52. Finding yourself more sociable and good humoured than usual

( )	( )	( )	( )
Have not had this symptom	Slightly felt	Moderately felt	Severely felt

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

53. Feeling inattentive and ineffective

( )	( )	( )	( )
Severely distressed	Moderately distressed	Slightly distressed	Have not had this symptom

At what time was this noticed (approximately), after administration of the drug?

( ) 10 minutes ( ) half an hour ( ) an hour
( ) 3 hours ( ) 6 hours ( ) 12 hours

2. THE CONSTRUCTION OF THE QUESTIONNAIRE

Perhaps the ideal way to study placebo responses would be for the experimenter to observe the subjects for long periods of time, after giving them placebo. In this way any physiological changes would be apparent at first-hand, and the subjects could be questioned closely as to their reactions. This would enable detailed and subtle information to be collected.

However this approach was rejected as impractical in the present experimental situation. The subjects used were all undergraduates, and it is obvious that students are not available for the periods of time needed. A compromise was therefore reached. It was decided to keep each subject under observation for a minimum period of an hour after administration of placebo. In addition, a wide selection of psychological and physiological feeling-states was ensured by means of a questionnaire. This was adopted because it is a convenient method of measurement and it has been used sufficiently often in pharmacological experiments for us to have confidence in it. Also it was felt that having a subject make repeated reference to a questionnaire was the best possible alternative to actual questioning by the experimenter.

The list of possible responses, given by subjects in reaction to a placebo, which might be of importance, is

almost endless. In presenting the subjects with a list of possible symptoms, many disadvantages arise. Firstly, this could restrict the subject's choice, and expression of, symptoms. It was hoped to overcome this disadvantage by:

(1) Using as a basis for the questionnaire, symptoms reported by previous experimenters.

(2) Using as wide a range as possible of different types of symptoms.

(3) Asking the subjects to make a note of all symptoms felt, which were not listed on the questionnaire. It was explained to them that, 'since the drug was relatively new, and because of the possibility of individual differences in response,' allowance must be made for symptoms not listed on the questionnaire.

(4) Having contact with the subject for a minimum of one hour after administration of placebo, so that reactions may be verbalised in some detail.

The second disadvantage of presenting subjects with a list of possible symptoms is that it could be suggestive of types or trends of symptoms. This, of course, can never be completely eliminated. However it was hoped this problem was minimised by witholding from the subjects details about the specific nature, purpose and modes of action of the 'drug' used in the experiment, and also by

providing as wide a range as practicable of possible reactions.

The third problem involved in the use of a questionnaire is that of its validity. This cannot be satisfactorily answered. However, a test retest measure of reliability was available because of the administration of the questionnaire over a four day period.

Questions relating to types of reactions or symptoms were derived from three sources. Firstly, from a table presented by Abramson et al., (1955) of the number and percentage of twenty-eight subjects responding positively to the items of the questionnaire used to measure placebo reaction. Since no more than 60 percent of the subjects responded to an item at any one time, the majority of questions eliciting a response of from 30 to 60 percent, were used.

Secondly, items were chosen from tables presented by Beecher (1959) reporting the frequency of occurrence of volunteered responses under placebo.

Thirdly, questions were compiled from personal judgement, based on impressions gained from various sources in the literature, in particular from the questionnaire used by Gliedman et al., (1958).

The result was a questionnaire containing fifty-three items, with approximately twenty-eight items devoted to

an assessment of physiological reactions, and twenty-five to psychological or emotional feeling-states.

The complete questionnaire may be seen in Table 9.

The questionnaire was designed to evaluate:

1) The frequency of response;
2) the frequency of change of response;
3) the degreee of amplitude of response;
4) the latency of the response.

1) The Measurement of Response Frequency

As far as could be ascertained from the literature, the method of total response frequency has been that used to measure placebo reaction. In experiments such as those undertaken by Jellinek (1946); Lasagna et al., (1954); Wolf et al., (1957); and Gliedman et al., (1958), degree of reaction to placebo consisted of the number of responses alleviated or inhibited after the ingestion of placebo.

However, it is the writer's thesis that, firstly, it would seem unnecessarily restrictive to limit the study of reaction to placebo to either the production of symptoms or responses, or the alleviation

or inhibition of symptoms or responses. 'Reaction to placebo' would be defined in the present study as any response (or symptom) reported by an individual after the ingestion of placebo. To specify the direction of reaction would appear rigid to the point of ignoring the obvious. In the clinical situation, for example, where the experimenter was interested only in the alleviation of certain responses, any subject who produced toxic symtoms in response to placebo would be labelled a non-reactor, because of lack of predicted symptom relief, when he was quite obviously a reactor to placebo. It would seem that a preferable method of studying the reactor to placebo, per se, was to make use of an experimental design which allowed for the administration of a placebo which carried no specified drug name, in this way minimising the possibility of symptoms being reported as occurring in a certain (expected) direction, or of a certain (expected) type. This would also eliminate the need for designating placebo reactions as 'positive' or 'negative' according to the 'direction' of response (i.e. response inhibition or response generation). In the present experimental design it was hoped that the use of an unnamed 'drug' would allow for the

reactor to placebo to report either response inhibition or response generation. This leads us to the second major criticism to be made against previous studies.

All experimental work surveyed in Section I measured and defined reaction to placebo by frequency of reported responses or frequency of responses inhibited, yet failed to observe if the subjects reported similar effects without taking placebo. We would maintain that some subjects (for example, those, in particular, who are high anxious) would report a large number of these symptoms without taking placebo (see Hypothesis IV). This would point to the need for a control study, as provided by the present experiment, where the frequency of symptoms reported by subjects who were not being administered placebo, was measured. This method of approach to the study of placebo reaction would enable a difference figure to be found, when the total number of responses reported pre-placebo was compared with the total number reported under placebo. However, it would be maintained that this is still a grossly inefficient measure of placebo reaction. Such a method disguises the specific results of individuals. Any one subject may, by using this system of measurement, be labelled as a non-reactor,

because there was no difference in the total number of symptoms reported under the pre-placebo condition as compared to the placebo condition. However, this same subject may have reported an entirely new set of symptoms under the placebo condition, but which still equalled the pre-placebo symptoms in number. The essence of the reaction in this case then, is changed. We would assert that the use of frequency of response change shown by individuals is a more subtle, accurate and logical method of measurement in placebo studies than those used so far.

This criticism might be most clearly demonstrated by use of results gained from the administration of the questionnaire used in the present study, to measure reaction to placebo. The frequencies of the subjects' responses to each item, reported over all eight days of the experiment, were used.

Response Frequencies Shown by the Experimental Subjects

The day by day frequencies of response to each item of the questionnaire for the eight days of the experiment is reported in Appendix B. The percentage of subjects' responding to each question is also shown.

From these results, Tables 10 and 11 were formulated. These show the items of the questionnaire which received the greatest mean percentage response (i.e. over each

condition of four days). Between twenty and seventy-eight percent of the experimental subjects consistently gave positive responses to twenty-two items of the questionnaire under the pre-placebo condition. In comparison, between twenty and fifty-five percent of the same subjects consistently gave positive responses to fifteen items in the questionnaire under the placebo condition.

Graphed distributions of response frequency shown by the forty-five experimental subjects who answered the items of the questionnaire under the pre-placebo condition, and graphed distributions of response frequency shown by the forty-four * subjects who answered the items of the questionnaire under the placebo condition, are reported in Appendix B. The graphed mean percentage of subjects responding positively to the items of the questionnaire, on all four days over the two conditions, may be seen in Figures I and II.

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* One subject left the experimental situation after a single placebo administration because of exceptionally toxic reactions and could not be replaced. For most statistical purposes however, the subject's result was included as an average.

FIGURE I: The Mean Percentage of 44 Subjects Responding Positively to the Items of the Questionnaire on all 4 Days while receiving placebo.

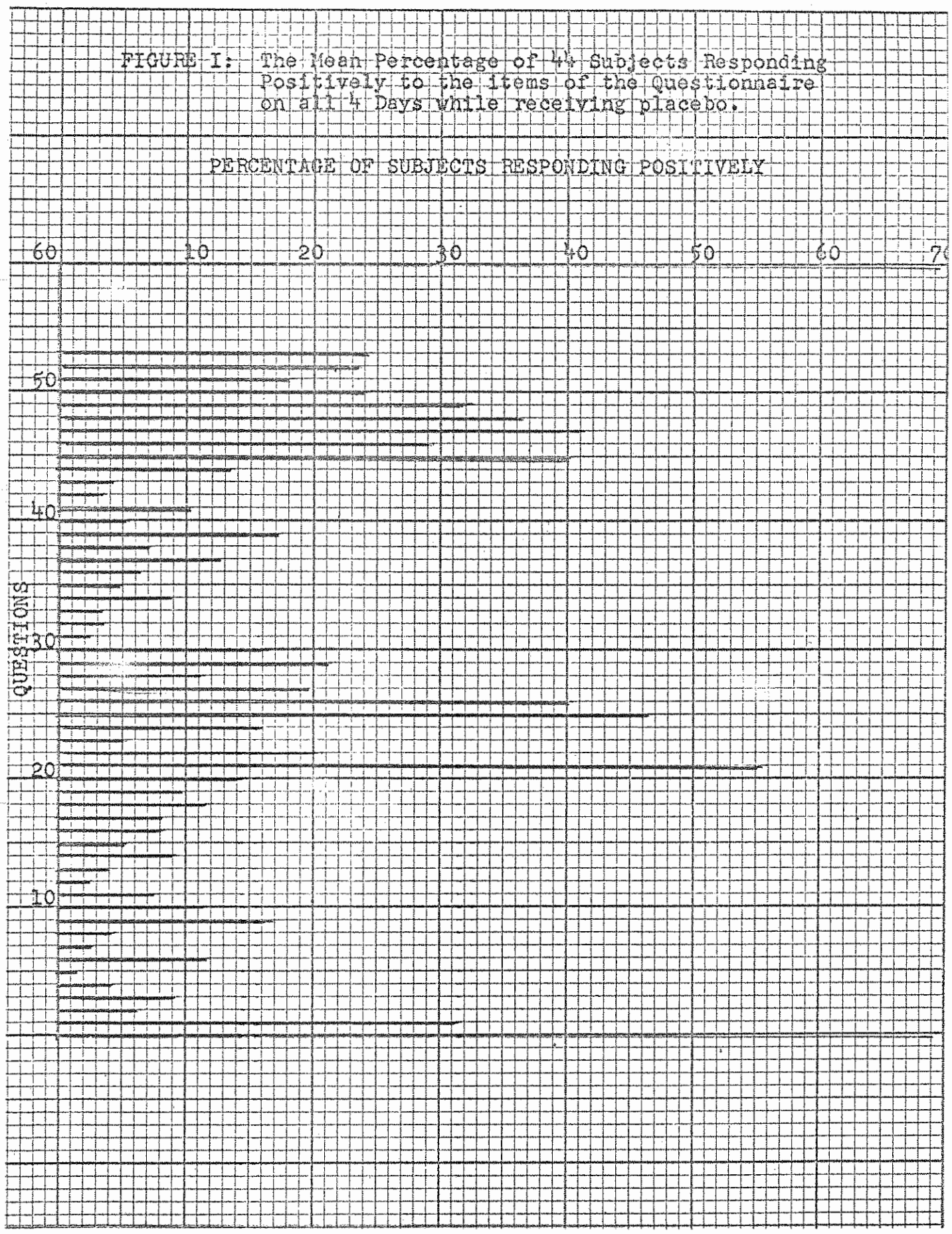


FIGURE 2: The Mean Percentage of 45 experimental subjects responding positively to the items of the Questionnaire on all 4 days of the pre-placebo condition

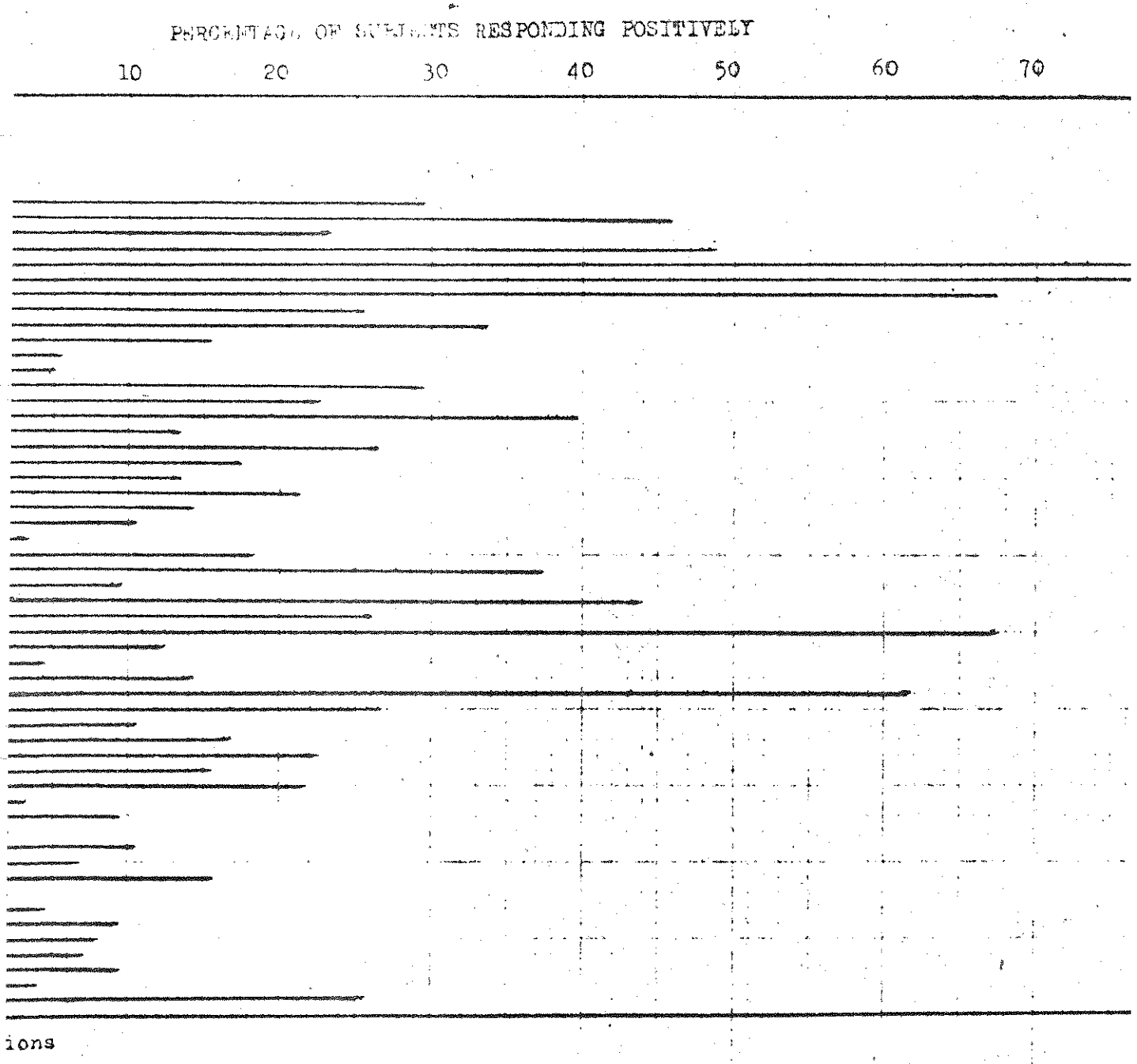


TABLE 10: The twenty-two items of the questionnaire to which the greatest mean percentage of experimental subjects responded under the pre-placebo condition of four days.

Item No.	Item	$\bar{X}$ % Response
48	Feeling enthusiastic and interested	78.0
49	Feeling co-operative	77.0
47	Feeling rested and contented	67.2
25	More than usually relaxed	67.2
21	Drowsiness or fatigue	61.7
50	A sense of restlessness	48.7
52	Finding yourself more sociable and good-humoured than usual	46.0
27	Feeling a warm glow	44.0
39	Feeling easily annoyed or irritated	39.7
29	Feeling blue	37.2
45	Feeling your mind was slow and sluggish	33.7
53	Feeling inattentive	29.7
41	Feeling critical of others	29.5
20	Increased appetite	26.7
37	Feeling lonely	26.2
26	Sensation of heaviness in your head or limbs	26.0
46	Feeling indifference or lack of concern	25.2
1	Headaches	25.2
51	Feeling confused and unreal	23.2
17	Nervousness and shakiness under pressure	22.5
15	Skin eruption or rashes	21.7
34	Your "feelings" being easily hurt	21.2

TABLE 11: The fifteen items of the Questionnaire to which the greatest mean percentage of experimental subjects responded under the placebo condition of four days.

Item No.	Item	$\bar{X}$ % Response
21	Drowsiness or fatigue	55.7
25	More than usually relaxed	46.5
47	Feeling rested and contented	41.7
26	Sensation of heaviness in the head or limbs	40.7
45	Feeling your mind was slow and sluggish	40.5
48	Feeling enthusiastic and interested	36.5
49	Feeling co-operative	32.5
1	Headaches	31.7
46	Feeling indifference or lack of concern	29.7
50	A sense of restlessness	24.7
53	Feeling inattentive	24.7
52	Finding yourself more sociable and good humoured than usual	24.0
29	Feeling blue	22.5
22	Difficulty in focusing your eyes	20.7
27	Feeling a warm glow	20.0

These results would appear to clarify the earlier point, that to make use only of symptoms reported after ingestion of placebo, without recourse to a control study to measure symptom frequency without placebo, (as has been the case in all earlier studies in this area), may lead to erroneous conclusions.

Turning first to Table 10, the type of symptom reported is of much interest and relevance. For example, most workers, when testing the effects of either a drug or a placebo, would accept items 15, 17, 26, 45, 1, 29 and 51, as physiological or psychological manifestations of toxic reactions; yet these symptoms were reported by subjects who were merely filling in the questionnaire, influenced neither by an active drug nor placebo. It would appear obvious that extreme caution is needed, by making use of control studies in any experimental design being used for the study of placebo (or active drugs.) This point might be further clarified by the use of comparisons with previous studies. Altogether twelve questions were used in the present questionnaire, which were selected from those reported by Abramson et al., (1955). Of all those studies from which questionnaire items were drawn, only Abramson's used placebo, and not placebo alternated with active drugs. For this reason, comparative figures of response frequencies found by the

present study, and by Abramson's, have been included. It must be noted, however, that Abramson did not make use of a comparative control group to measure pre-placebo responses.

Table 12 reports comparative percentages of response frequencies shown by the subjects used in Abramson's study, (for one occasion only, under placebo and the first administration) and the subjects used in this study (for the first day of the placebo condition, [which was actually the fifth administration of the questionnaire] and the first day of the pre-placebo administration).

TABLE 12: A comparison of percentage frequencies of response to 12 items of a questionnaire used by Abramson et al., (1955) and the present study, with 28 and 45 subjects respectively.

Item		% Response First Administration Placebo Condition Abramson et al.	% Response Pre-placebo Day 1 Thorn	% Response Placebo Day 1 Thorn
20	Increased appetite	25	27	22
1	Headaches	50	49	27
3	Heart pounding or racing	15	10	2
4	Trouble getting breath	5	7	4
6	Nausea or upset stomach	28.6	10	15
14	Difficulty in swallowing	20	3	11
19	Moistness of palms	60.7	11	9
21	Drowsiness or fatigue	50	62	68
22	Difficulty in focusing eyes	5	14	25
24	Increased thirst	15	12	15
26	Sensation of heaviness in head or limbs	25	26	36
9	Faintness or dizziness	28.6	16	13

These results would seem to provide a very clear case for the use of a control study in experiments with placebo, and also with active drugs. From the results reported in Tables 10, 11 and 12, it is clear that the administration of placebo in this study was not proven to be either a necessary or sufficient condition for a group of women undergraduates to report the occurrence of symptoms commonly regarded as toxic. In addition, the results reported by Abramson et al., as indicative of placebo reaction having occurred because a number of symptoms were reported after the administration of placebo, must be rejected unequivocally. It is clear that the frequency of reported symptoms for the first day of the pre-placebo condition in the present study is much closer to those figures reported by Abramson for the first day of placebo administration. Abramson's first measure of response frequency is a more similar situation to the first measure of response frequency, without placebo, in the present study, than that taken while placebo was being administered. Because the results reported in Tables 11 and 12 show that subjects will report a large number of symptoms under 'normal' conditions no conclusions can be drawn from any study such as Abramson's which uses frequency of responses reported under a placebo (or drug) condition only.

In view of the precautions taken in the present study, and the fact that so many subjects reported 'toxic' symptoms in the control situation, a partial rejection might well be made of the results of all studies reported in Section I, in the survey of literature on the placebo problem, for ignoring the necessity for a comparative control situation. It is obvious, that despite a 'general feeling' otherwise, subjects report many more toxic symptoms from day to day, under 'normal' circumstances, than has been admitted or realised in the field of placebo research. It is not enough to assume that toxic symptoms are produced merely by ingestion of either an active drug or placebo. Neither is it enough to assume without testing the assumption, that subjects who report any type of symptom after ingestion of an active drug or a placebo, are behaving in a manner which is markedly different from their normal response pattern. Some measure of day to day occurrence of such symptoms is a necessity, before the experimental variable is applied, whether the experiment is in the field of clinical or experimental pharmacology or personality theory.

Turning now to the symptoms reported under the placebo condition of the present study, it will be seen that they were not necessarily the same as those reported under the pre-placebo condition. The changes were examined to see whether particular symptoms were typical

of placebo reaction.

Using the Day 4 pre-placebo responses as a comparative base line, these were compared for change with those symptoms reported by the subjects to items of the questionnaire under the placebo condition, on Day 1. The McNemar Test of the Significance of Changes was used in order to establish if the symptoms reported on Day 4, pre-placebo, were actually responded to in a different way while the same subjects were receiving placebo. The items which showed a significant change, and the direction of their change, are shown in Table 13.

TABLE 13: The results of a test of the significance of change of responses, with the direction of change, reported by 45 experimental subjects to 53 items on Day 4, pre-placebo, and Day 1, placebo.

No.	Item	Direction of Change	χ^2	p
48	Feeling enthusiastic and interested	Negative	15.2	.001
49	Feeling cooperative	Negative	12.5	.001
52	Finding yourself more sociable and good humoured than usual	Negative	6.5	.02
15	Skin eruptions or rashes	Negative	7.00	.01
26	Sensation of heaviness in your head or limbs	Positive	8.04	.01
37	Feeling lonely	Negative	9.00	.01
38	Feeling compelled to ask others what you should do	Negative	4.00	.05
50	A sense of restlessness	Negative	16.00	.001

These items must be subjected to closer analysis. Of the 8 items out of 53 which showed any significant change, only three, Item 48 (feeling enthusiastic and interested), Item 49, (feeling cooperative), and Item 52, (feeling yourself more sociable and good-humoured than usual,) seemed to belong to any grouping. The total

change of the group, (35.5) was significant at the .001 level. The direction of change was negative. That is, the experimental subjects felt themselves less tractable and outgoing after the first day of administration of placebo.

There are two possible explanations for this result. Either the giving of placebo had this effect, or it was the result of the experimental situation, i.e. as the experimenter did not tell the experimental subjects that they were involved in a "drug" study until the first appointment for administration of the"drug", they were suddenly precipitated into an anxiety-provoking and generally rather fear producing situation, and it is understandable that their feelings of cooperation and enthusiasm would wane rapidly.

The most logical interpretation would appear to be that the change shown in this group of responses was attributable to the emotional overtones of the experimental situation per se, and not to the administration of placebo.

As far as the remaining items are concerned, little pattern is discernable in the reporting that subjects got fewer skin disorders, felt less lonely, felt less compelled to ask others what they should do, and felt less restless, as compared to feeling a greater sensation of heaviness in the head or limbs - all after receiving placebo.

If the change in response to these items was the result of the administration of placebo, then the change should be consistent when responses reported on Day 2, placebo, were compared with responses reported on Day 4 of the pre-placebo condition. Results are reported in Table 14.

TABLE 14: The results of a test of the significance of change of responses reported by 45 experimental subjects to 8 items on Day 4, pre-placebo, and Day 2, placebo, (only those items which reached a significant level of change are shown.)

No.	Item	Direction of change	χ^2	p
15	Skin eruptions or rashes	Negative	9.00	.01
26	Sensation of heaviness in the head or limbs	Positive	19.7	.001
48	Feeling enthusiastic and interested	Negative	17.1	.001
49	Feeling cooperative	Negative	17.6	.001
50	A sense of restlessness	Negative	4.08	.05
52	Feeling sociable and good-humoured	Negative	10.8	.001

It can be seen from Table 14, in comparison to Table 13, that six out of eight of the symptoms changed, with the direction of change being maintained. Assuming that there is agreement with the writer that the change in items 48, 49 and 52 was caused by the subjects' antipathy to the experimental situation, these results show that only three symptoms changed out of the remaining five, which changed from Day 4, pre-placebo, to Day 1, placebo. That is, three out of a total of fifty-three items in the questionnaire showed a consistent pattern of change. This is obviously too small a number to be regarded as a significant result and does not warrant study in greater detail.

It might now be seen that using the method of total frequency of change in response to measure and define placebo reaction is of little use. All that the above approach to the analysis of results could show was that certain items were more frequently responded to than others in different experimental conditions. It tells us nothing about individual reactions to placebo. The only conclusion which can be drawn from the above method of analysis of results is that placebo reactors, if they exist, do not report changes in a consistent set of items.

It can now be seen that the use of response frequency as a measure or definition of reaction to placebo is a

useless method of approach. Its lack of use is also aggravated by experimenters ignoring the need for control studies, when studying response to placebo. Having outlined the disadvantages of previous methods of approach, the advantages of the present experimental design should be all the more clear.

The method of total response frequency was rejected as a measure, in the present study, and the total number of changes in response to each item of the questionnaire, in either direction, reported by each individual subject, using the pre-placebo response score as a comparative base line, served as the measure of placebo reaction.

That is, each subject was given a score, called her placebo reaction score, which comprised the total frequency of changes in response to all items of the questionnaire, when the symptoms reported for Day 1, for example, of the placebo condition, were compared with those reported for Day 4, for example, of the pre-placebo condition. That is, if a subject reported having a symptom on Day 4, pre-placebo, which she did not report while taking placebo on the first day of that condition, then this would be counted as a single score, toward a total score of placebo reaction. If, conversely, the same subject reported a symptom while on placebo that she did not report while in the pre-placebo

condition, this would also rate as a single score, as change had occurred. In this way, allowance was made for the reactor to placebo to acquire or lose symptoms as a result of taking the placebo, and a score be derived from the total number of changes. This method was considered essential in view of the disadvantages of previous methods, and also because the experimenter gave the subjects a placebo labelled as an unknown drug. This meant that no special acquisition or loss of symptoms was expected. If subjects reacted to the administration of placebo, both must be expected as types of reaction. In this way it was hoped to demarcate those individuals who were capable of reacting to placebo per se, not necessarily just responding to suggestions that expected symptoms should occur. The data provided by the matched control group was also scored in this way, and a mean score was found.

The validity of the placebo reaction score was checked by comparing the mean reaction score of the experimental group with this mean score. If the score were sensitive to reaction to placebos it would be significantly higher for the experimental group where a placebo was administered than for the control group where there was only a comparable time lapse, but no placebo was given.

2) The Measurement of the Degree or Amplitude of Response

It is obvious that some differentiation of degree of reaction to placebo must be made, as a relationship could exist between amplitude of response and individual differences on the personality variables being used.

The rating scale technique was adopted, as it seemed most suited to assisting a subject who had difficulty in verbalising effects, or conversely, set a limit upon the subject prone to exaggerate such effects. Also, this method had been used by such workers as Beecher (1959) and Gliedman et al., (1958). As had been discussed elsehwere, lack of uniformity in methods prohibits direct comparison of results in this area of research.

In responding to the questionnaire, the subject's task was to choose from four points on the scale the one most accurately corresponding to her current subjective state. The points on the scale ranged from, "Have not had this symptom," through "slightly distressed" and "moderately distressed" to "severely distressed." Scoring ranged from 0 for "Have not had this symptom" to +3 for "severely distressed."

3) The Measurement of the Latency of Response

Beneath each item on the questionnaire a time scale was provided, with the question, "at what time was this [effect] noticed (approximately) after administration of the drug?" The time intervals ranged from ten minutes to twelve hours and may be seen in detail in Table 11. The time scale's main purpose was to help create the atmosphere of a genuine drug study where stringent methods of appraisal, such as a check on the time intervals at which symptoms occured, are very important.

Subjects were instructed at all times to regard the listed time intervals as purely indicative and not totally restricting. They were encouraged to report the appearance of placebo reactions at more specific time intervals if they so desired.

The Pre-Placebo or Control Questionnaire

This questionnaire was identical to that used while subjects were administered placebo, with two exceptions. The instructions were, of necessity, different, and may be seen in Table 15; and no time scale was added, as the absence of the relevant variable i.e. the placebo, rendered this unnecessary.

TABLE 15: Instructions for the Pre-placebo control questionnaire.

NAME: _____

DATE: _____

INSTRUCTIONS

Listed below are a number of symptoms or problems that people sometimes have. Directly under each symptom or problem is a scale showing how affected or distressed a person may feel as a result of having the particular symptom. Please read each of them carefully and decide whether you had the symptom during the past twenty-four hours.

If you have not had the symptom at all during the past twenty-four hours, place an X in the parenthesis above the statement "Have not had this symptom" in the scale. If you have had the symptom one or more times during the past twenty-four hours, then decide whether the symptom was slightly, moderately or severely distressing and place an X in the parenthesis above the statement which most nearly describes the amount of distress, worry or suffering you experienced. SINCE THE SAME STATEMENT IS NOT IN THE SAME PLACE ON EACH SCALE, PLEASE READ EACH ONE CAREFULLY.

Example: If you were severely distressed by a headache during the past twenty-four hours, then in completing the scale number 1 regarding headaches, you would place an X over the statement "severely distressed"

TABLE 15 cont.

as indicated below.

1. Headaches.

( )	( )	( )	(X)
Have not had this symptom	Slightly distressed	Moderately distressed	Severely distressed

If you have been slightly distressed by pains in the head or chest, then in completing scale number 2 you would enter an X in the parenthesis ( ) over "slightly distressed" as indicated below.

2. Pains in the heart or chest.

( )	( )	(X)	( )
Severely distressed	Moderately distressed	Slightly distressed	Have not Had this symptom

Do not spend much time on any one question. Before you hand in your completed questionnaire, please check to see that you have answered every question.

4. THE PLACEBO

The vehicle of presentation of placebo is of the utmost importance as Leslie (1954) and Shapiro (1960) testify. Recently the influence of size, colour, and teste on the effectiveness of placebo has been discussed, although as has been pointed out, "What constitutes a good placebo cannot be specifically stated, because what may be a good one for one patient may not be so for another even though he has a similar condition." (Editorial, Journal of the American Medical Association, 1955, p.780.)

Colour of the capsule is important. "A capsule coloured red, blue or yellow suggests specific attributes which a colourless capsule containing a white powder might seen to lack." (Leslie, 1954, p.860.) Leslie advises the use of red, yellow or brown rather than blue or green which are associated with "poisonous or external-use-only liquids." (Ibid.) He feels that the size is also important, tiny and oversize tablets being much more impressive than average sized ones, "..... the tiny ones suggesting great strength and the jumbo ones impressing by its heroic size." (Ibid.)

The more a tablet resembles aspirin the less effective the psychological effect. Also, "It is probable that prescribing nine or eleven drops rather

than the usual ten would add to the effectiveness of the placebo effect." (Shapiro, 1960, p.119.) Taste has always been important. The aromatic elixir (Wolff, 1946); the compound tincture of gentian (Dubois, 1946; Findley, 1953; Leslie, 1954; Wolff, 1946), and asofetida were standard bitter placebo medications used in the past. It may be pointed out that the simple lactose tablet has fallen into disuse because it can be easily recognised and because it can be tasted.

Bearing all these relevant factors in mind, it was decided to use a 1 grain capsule of standard manufacture[1] which was coloured red. As lactose powder would have diminished the colour effect by making it pale pink, red jelly crystals were substituted for the capsule contents. Care was taken that each capsule was adequately filled, so that there were no marked differences in appearance.

Because of the use of jelly crystals, subjects were instructed not to bite the capsule, but to swallow it straight down. In this way it was hoped to avoid any subject tasting the all-too-familiar crystals. This was aided by capsules which were rather slow in dissolving.

A capsule seemed a more legitimate choice than either a tablet or a liquid. Firstly, because capsules are associated, in this country, with newer and more potent drugs.

---

[1] Supplied by Parke Davis Ltd.

Secondly, because through the medium of a coloured capsule, the subject could be more impressed with its potential efficacy rather than with that transmitted by a more indiscriminate tablet. Thirdly, because it allowed for easy manufacture, procurability, storage and administration.

5. THE POST-EXPERIMENTAL ENQUIRY

Many subjects display an intense concern with the successful completion of the experiments in which they participate. The volunteer subject, especially, has a positive orientation to research and wants to contribute to it by means of his performance in the experiment. However, as far as the subject is concerned, he is contributing to research only to the extent that his participation is useful in making the experiment 'work.'

For an experiment to work means, as a rule, that the experimenter demonstrates what he sets out to prove. The subjects thus acquire an investment in confirming the experimenter's hypothesis.

It has long been recognised that the subject's knowledge about the purpose of experimental work may play a role in his behaviour. The subject will utilize whatever cues are available in order to formulate his own idea of what the purpose of the experiment is.

Even in a study such as the present one, where the true experimental purpose is disguised, there may be aspects of the experimental situation which communicate to the subject the experimenter's wishes and hypotheses. These cues, or demand characteristics, where discussed

earlier (see p.107.)

In order to determine the demand characteristics of an experimental design, it is necessary to determine how subjects perceive the experiment in which they are participating, in terms of its purpose and the experimenter's hypothesis. The most practicable, and, in many ways, most efficient way of determining these perceptions is by enquiries which elicit this information after the subject has completed the experiment.

The following questions were used as a basis of the post-experimental enquiry, and were adopted from Orne.

1) What do you think this experiment is about?
2) What do you think this experiment is trying to demonstrate, what do you think I expect to prove, in other words what is my hypothesis?
3) What do you think we will find, in other words, what is your hypothesis, having taken part in the study?
4) What do you think others have done or will do in this experimental situation?
5) What do you think you did?

(Orne, 1959, p.8).

The present writer is in complete agreement with Orne's theoretical standpoint, and it is felt that the approach is particularly relevant to an experiment such as the present one. Therefore it was decided to adopt Orne's method of post-experimental enquiry, using his suggested points as the basis of the interview procedure.

Each subject was taken to an interview room, and the subsequent enquiry was tape recorded. Apart from structuring the interview around the questions suggested by Orne, each subject was asked:

1) What previous experience have you had in
   a. taking drugs
   b. administering drugs

2) What type of drug do you think was used in this study?

(No specific or technical names are required.)

3) Did you at any time during the experiment hear of other people's reactions to the drug or discuss your own with friends?

Orne drew attention to the fact that a subject's initial response to such questions, "in the majority of all cases, will be 'I don't know'," (Orne 1959, p.8) and "the experimenter should not breathe a sigh of relief and go on to the next question, but should "push" the subject, forcing him to guess, etc." (Ibid.)

Bearing this in mind, the experimenter sought as much detail as possible from the subjects. The format of a typical interview may be seen in Appendix A.

6. THE SUGGESTIBILITY TESTS

When the post-experimental enquiry interview was completed, each subject was then given the battery of suggestibility tests.

1. The Test of Arm Bending Suggestibility

The subject was seated in a chair. A revolving arm rest was attached to the side of it. Any movement of the arm resulted in a corresponding movement of the rest. The apparatus may be seen in Plate II. It was suggested to the subject for a period of two minutes, that she would feel her arm "moving further and further round, over your body." The test was scored by a rating scale method, ranging from "No response (0) to a "Maximum Fast Response (6). Scoring details are presented in Appendix A.

2. The Test of Body Sway Suggestibility

The subject was required to stand on the base of the body sway apparatus (Plate I) and a measurement of height was made. A thread, coiled round a 6" diameter wheel was attached to the subject's collar. A recording of forward movement was obtained by means of a weight, attached to the end of the thread, which moved up or down a measuring rule attached to the apparatus.

The subject was told to stand, in an ordinary manner, with her hands by her side and her eyes closed, for thirty seconds. This was to gain a measure of static ataxia. It was recorded by means of the apparatus.

It was then suggested that the subject would feel herself falling further and further forward. The instructions were:

"Now keeping your eyes closed, you are swaying forward ..... swaying further and further forward..... your whole body is moving forward ..... swaying further forward ....." These suggestions were continued for ninety seconds and an attempt was made to be neither too authoritarian nor too coaxing. The maximum response in inches was obtained, appropriate correction being made for the subject's shoulder height, and for static sway.

3. The Ink Blot Test (Eysenck, 1949).

In this test the subject was shown Card I from the Rorschach Ink Blot test (Eysenck and Furneaux, 1945) and told "people often see objects in these blots." Two common objects, a bat and a butterfly were mentioned. The subject was then told three further objects, a Bhudda, a space rocket and a steam train, which were as unlike anything in the ink blot as possible, but which were presented as quite usual responses. The subject was then asked whether she could see these things in the blot. The number of unusual responses seen constituted the score on the test.

4. The Heat Illusion Test (Eysenck, 1949.)

The apparatus used is shown in Plate III. The experimenter told the subject she was testing individual differences in heat threshold. The subject was asked to report when she first felt a sensation of heat from the metal handle in the front of the box. The handle was slowly heated by an electrical current passing through a resistance box. After two trials in this fashion, the

experimenter switched off the current by means of a hidden switch, and again invited the subject, for two trials, to report when she began to feel the heat. If the subject felt nothing within sixty seconds, a zero response was recorded. The number of times the subject reported a feeling of heat when objectively no heat was present constituted the score.

7. THE PROBLEMS OF MOTIVATION

It is recognised that some methods of approach are more successful than others in motivating subjects for participation in 'traumatic experiments' (cf. Orne, 1957). It is known that subjects do volunteer for psychological experiments and are willing, under certain circumstances, to tolerate states of extreme discomfort for experimental studies. Orne discusses some of the factors involved in the motivation of a subject population to take part in such experiments. He claimed that the situation should have three aspects: that of motivating the subject to complete the experiment; that of making the subject pleased at having participated in the experiment despite the anxiety involved; and that of encouraging subjects who could not endure the situation, not to regard themselves as failures.

In view of these points an attempt was made in the present study, to motivate the subjects to participate by firstly, involving them in the experimental situation at some length before revealing its main purpose. Before being told the experiment involved the testing of a drug, each subject had had positive contact with the experimenter, who maintained an enthusiastic attitude, encouraging subject participation.

The element of the unknown also appeared stimulating to the subjects. In addition, a total of seven rather lengthy questionnaires had been completed at this stage, which involved the subject not a little in the progress of the experiment, and each subject realised that to withdraw at this point meant the loss of a large amount of time and data.

Secondly, an appeal was made to each subject's pride; (e.g."University students are best suited to this type of study because they are, by training and ability, better able to report accurately their behaviour changes.") Also, an appeal was made to each subject's sense of usefulness and ability to make a practical contribution. That is, the importance of the drug in later use, once certain facts about it were established, was implied. A combination of these factors seemed to result in the majority of subjects staying in the experimental situation, despite varied amounts of apprehension. Post-experimental

enquiries revealed that the subjects, as a whole, were apprehensive of the possible effects of the drug, but had sufficient trust in the experimenter, as a representative of the Department of Psychology, to feel that the Department would not expose them to undue danger. However, the seriousness of the situation, as seen by the subjects, was not to be underestimated. Statements made by the subjects testified to this.

It was decided not to tell the subjects that an entirely new drug was being used, but a new type, derived from a drug already in existence, the effects of which were relatively well known. In this way we hope to avoid an over-traumatic experimental situation, and also, pushing the credence of the average undergraduate too far.

8. A DESCRIPTION OF EXPERIMENTAL PROCEDURE

As the method of selection of subjects has been described earlier (see p.129) this will not be repeated. Forty-five were selected, and of these, twenty-five, or 55 percent were non volunteers.

Each subject, after selection, was requested to fill in the pre-placebo control questionnaire (see Tables 9 and 15), once a day for four consecutive days. Care was taken to see that no subject was ill, menstruating or severely emotionally upset (as a result of extraneous circumstances) at these times. This was accomplished by scheduling subjects to fill in the questionnaire at other than these times. It was explained that the purpose of the experiment could not be revealed at this point, and this seemed accepted, and was not questioned by the subjects.

At this point, an appointment was made with each participant, at a time when she would be available for four days. It, was, of course, not possible to duplicate appointments at exactly the same time each day, but appointment times were kept as uniform as was practicable. Once again, care was taken to check whether this time coincided at all with menstruation or illness.

Each subject was also asked what drugs she was taking at the time. If any drug was being taken which

was more potent than, for example, aspirin, the subject was rejected. It is clear, that if a study is to be presented as one testing an active drug, no interaction effects can be allowed. This would also apply in the placebo situation, where the experimenter must be able to gauge placebo reactions without interference from legitimate drugs.

This, and subsequent experimental sessions were held in the experimenter's office. At one end was a table, part of which was covered with white towelling, on which stood apothecary jars containing the capsules, a jug of water and disposable cups. The subject was seated in a comfortable chair. She was then told the purpose of the study. It was explained that the experimenter was testing the behavioural effects of a relatively new drug as part of a combined research project, in connection with the manufacturers of the drug. University students were being used because of their superior ability to report carefully any changes which occurred as a result of the drug. A brief outline was given of the difficulties involved in testing new drugs (after they were proven fit for human consumption) on valid groups of people. The experimenter emphasised that the drug was not dangerous, but added that she was not able to wholly predict its effects, particularly in view of the possibility of

individual differences in reaction to it. It was explained that no details could be offered as to either the drug's nature or its possible effects, so that subjects would not form a priori assumptions about their reactions. Each subject's coöperation was then asked for.

Two subjects left the experimental situation at this point and were replaced by others with similar T.M.A.S. scores. Once the remaining subjects had agreed to participate further in the experiment, the following instructions were given.

Experimental Instructions

"The drug which I am going to give you is not particularly new and it is not dangerous. However, a great deal of research is still needed, especially in reaction to it. You may find that it has side effects, and whether these are of one type or another seems to depend on individual differences. The most important thing is that I want you to observe yourself very carefully. If you have taken aspirin, for example, you know that after a time period it has a certain effect on you, and then that this effect may lessen after a while

This is a process common to all drugs, including this one. The questionnaire which you have been given, and which you are to fill in, will help you to express, and rate on a scale, how you feel. When filling it in, I want you to note the approximate time period when you first feel the drug's effects. Make a note of all the changes you feel, regardless of whether you judge the drug to be responsible or not. Keep the questionnaire with you all during the day, in order to keep a record of your reactions. This is most important. It will be necessary to constantly remind yourself that you are still in an experimental situation.

If you become at all unhappy or worried about the effects of the drug, then contact me straight away.

Now I want you to swallow the capsule without biting or chewing it, and then sit down here and rest. All you will be required to do is to observe and record your reactions carefully, and I will help you with any problems that might arise in connection with the questionnaire.

It is also very important that you don't discuss this experiment with anyone else, or your reactions to the drug, as this can obviously influence other people's reactions.

If a subject experienced any marked untoward effects during the first hour, she was detained for a longer time. Two subjects returned during the course of the experiment, because of anxiety over symptoms, occurring after they had left the experimenter's office.

It must be acknowledged that an experimenter runs the risk of imprecise records when subjects are allowed unsupervised recording of symptoms. The problems involved in subjects noting their responses in their normal day to day circumstances, was explained to all participants in the experiment. The experimenter explained that unsupervised recording of symptoms was the only method practicable under normal circumstances, rather than the more artificial and confined circumstances of the experimenter's office. It seemed, from observation, that this explanation was accepted by the subjects, and motivated them to take some care in observation. For the first few hours after taking the capsules, the majority of participants remained in the normal University situation of working in the library or attending lectures. The questionnaires were conscientiously filled in even during lecture hours (a fact testified to from staff sources.)

In addition, the pre-placebo control questionnaire was completed day by day under similar circumstances.

When each subject had completed the four day course of placebo, a final appointment was made. Because of

the number of subjects involved in the experiment and the testing time consumed, for each participant, the final experimental session was held approximately three weeks later.

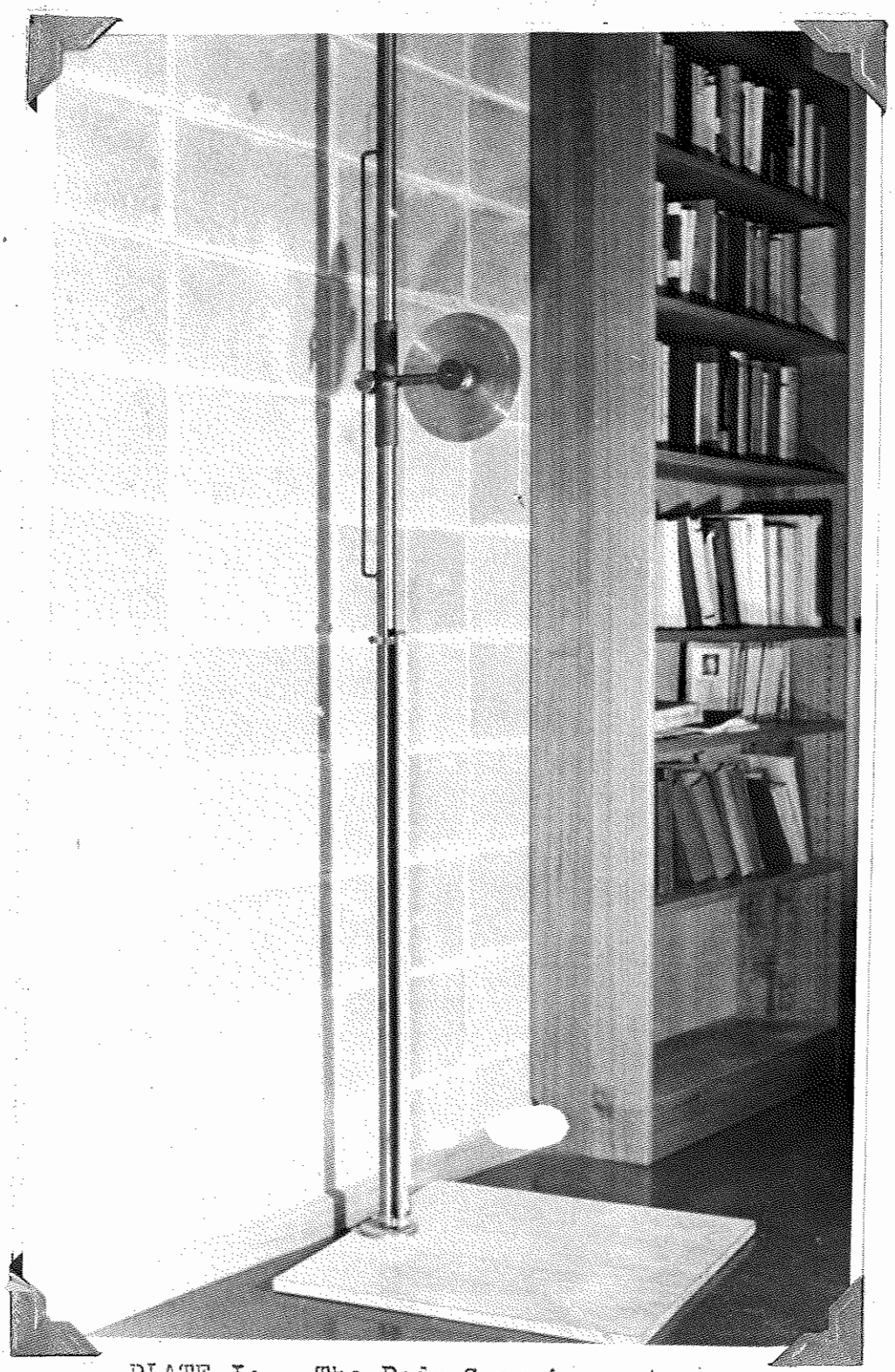


PLATE I: The Body-Sway Apparatus

PLATE II: The Arm-bending Apparatus

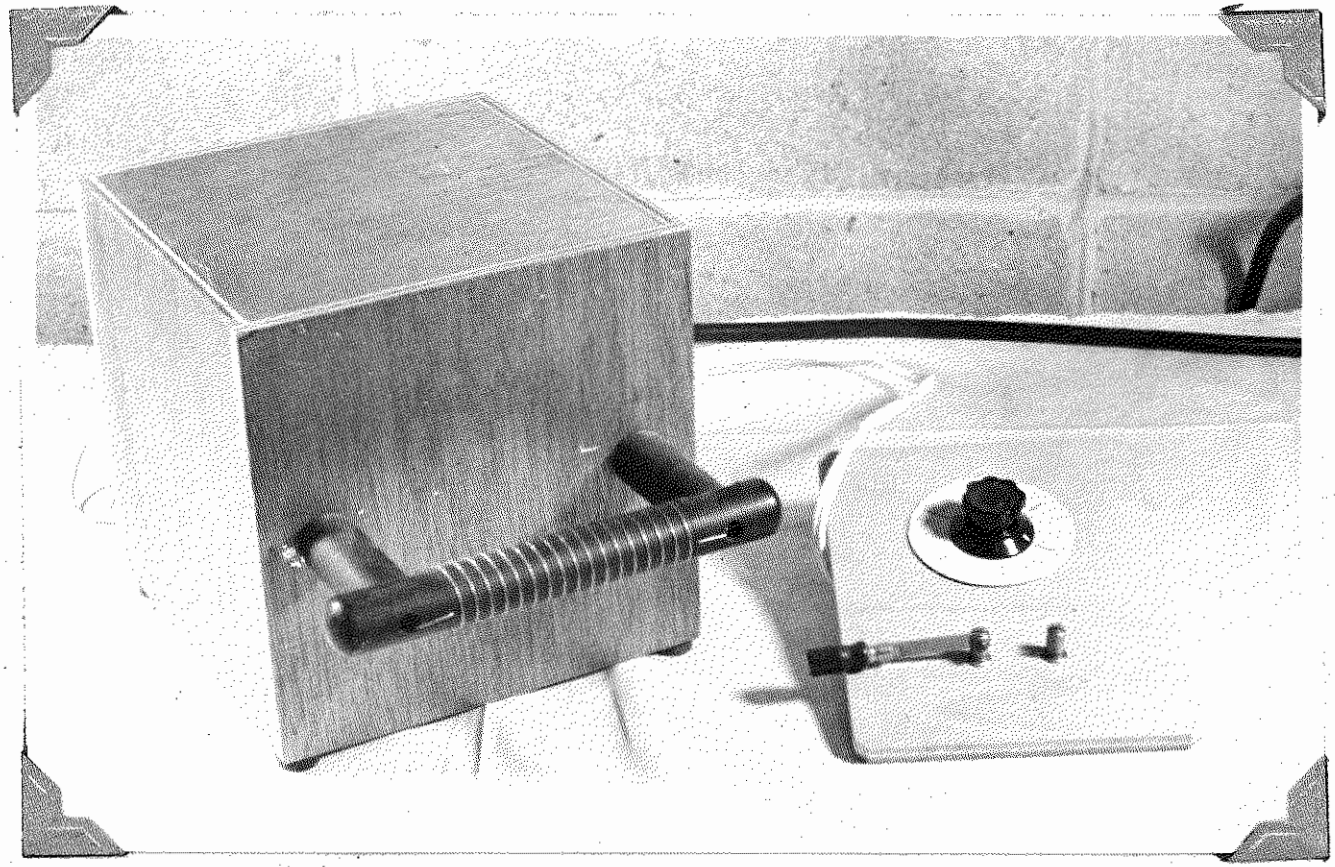


PLATE III: The Heat-illusion Apparatus

Page

SECTION III

THE RELIABILITY OF THE QUESTIONNAIRE

It is important that the questionnaire used in this study be a reliable measure, i.e. stable and dependable as a measuring instrument over the requisite time period. Test retest correlations of total responses obtained on each day with every other day, by the experimental subjects, under the pre-placebo and placebo conditions, are reported in Table 16. From Figure 3 and from Table 16, it is clear that the questionnaire is a reliable measuring instrument, although the reliability figures fall off with the number of days the questionnaire is administered.

FIGURE 3. Distribution of the mean number of symptoms reported by 45 subjects, under conditions of no placebo and placebo, for 4 days respectively.

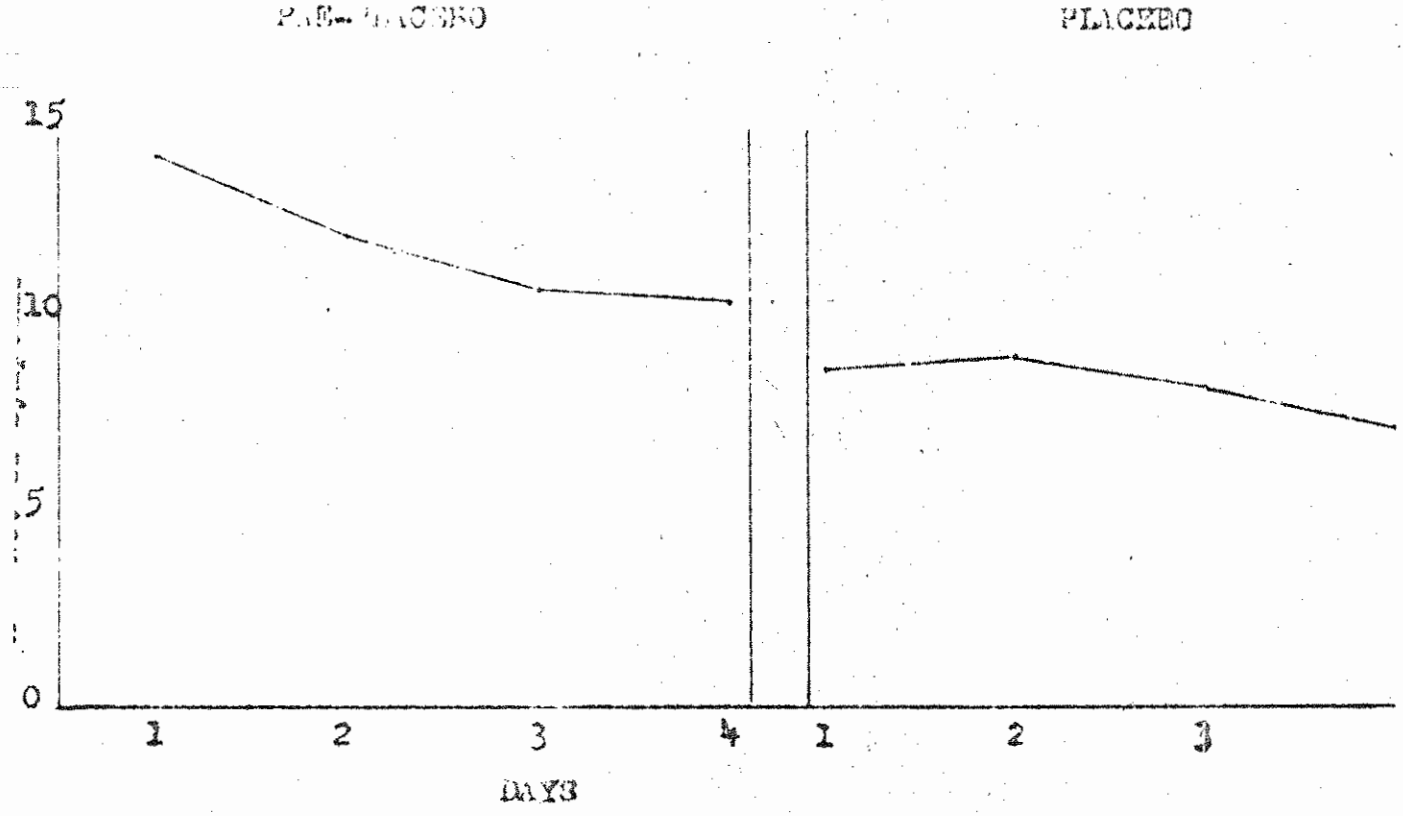


TABLE 16: Evidence for the reliability of the Questionnaire. Test retest correlations of total response frequency reported by the experimental group of subjects under conditions of no placebo and placebo over 8 days.

		Pre-Placebo (Days)				Placebo (Days)			
		1	2	3	4	1	2	3	4
Pre-Placebo	1	--							
	2	79	--						
	3	76	77	--					
	4	70	75	79	--				
Placebo	1	38	41	49	51	--			
	2	36	44	47	37	66	--		
	3	44	55	59	44	62	80	--	
	4	32	38	42	46	69	74	69	--

The greatest change in reported response frequency was between Day 1 and Day 2 pre-placebo, yet the reliability here is ·79. The reliability between Day 1 and Day 2 placebo is ·66. However, the reliability between Day 4, pre-placebo, and Day 1, placebo, is ·51, which would lead us to expect changes from Day 4 to 5 as the result of the introduction of placebo. This would seem to indicate that scores of placebo reaction in terms of change of response, as outlined earlier, are the necessary measures.

THE RESULTS

The Results of Testing Hypothesis I.

Hypothesis I states "That an experimental group of subjects to whom placebo is administered, will show more changes in symptoms, and intensity of symptoms, than a control group to whom no placebo was administered."

The testing of this hypothesis is, in essence, a test of the validity of the method of measurement of placebo reaction put forward in this study. It will be remembered that a change in response, in any direction, reported by the experimental group subjects, from the pre-placebo condition to the placebo condition, was defined as a placebo reaction. For this to be a valid measure of placebo reaction, a significant difference would have to be found between the mean number of response changes reported by the experimental group when compared to the mean number of response changes reported by the control group at equivalent time periods. The mean number of responses which changed for the two groups is reported in Table 17 .

TABLE 17: The Mean Number of Changes in Response to items in the questionnaire shown by the experimental and control group subjects from Day 4 to Day 5.

	Control Group	Experimental Group
$\bar{X}$	7.67	10.57
S.D.	4.17	6.23

A t test was carried out, and the difference between the means (for a one-tailed test) was found to be 2.28 ($.025 > p > .01$). It was concluded that the significantly higher number of changed responses reported by the experimental group of subjects was due to the administration of placebo. It would appear then, that the measure of placebo reaction was a valid one.

The proportion of experimental group subjects showing changes in response to items of the questionnaire, for the fourth day of the pre-placebo condition, to the first day of the placebo condition, compared with the proportion of control group subjects reporting changes from the fourth day to the fifth day, can be seen in Table 18.

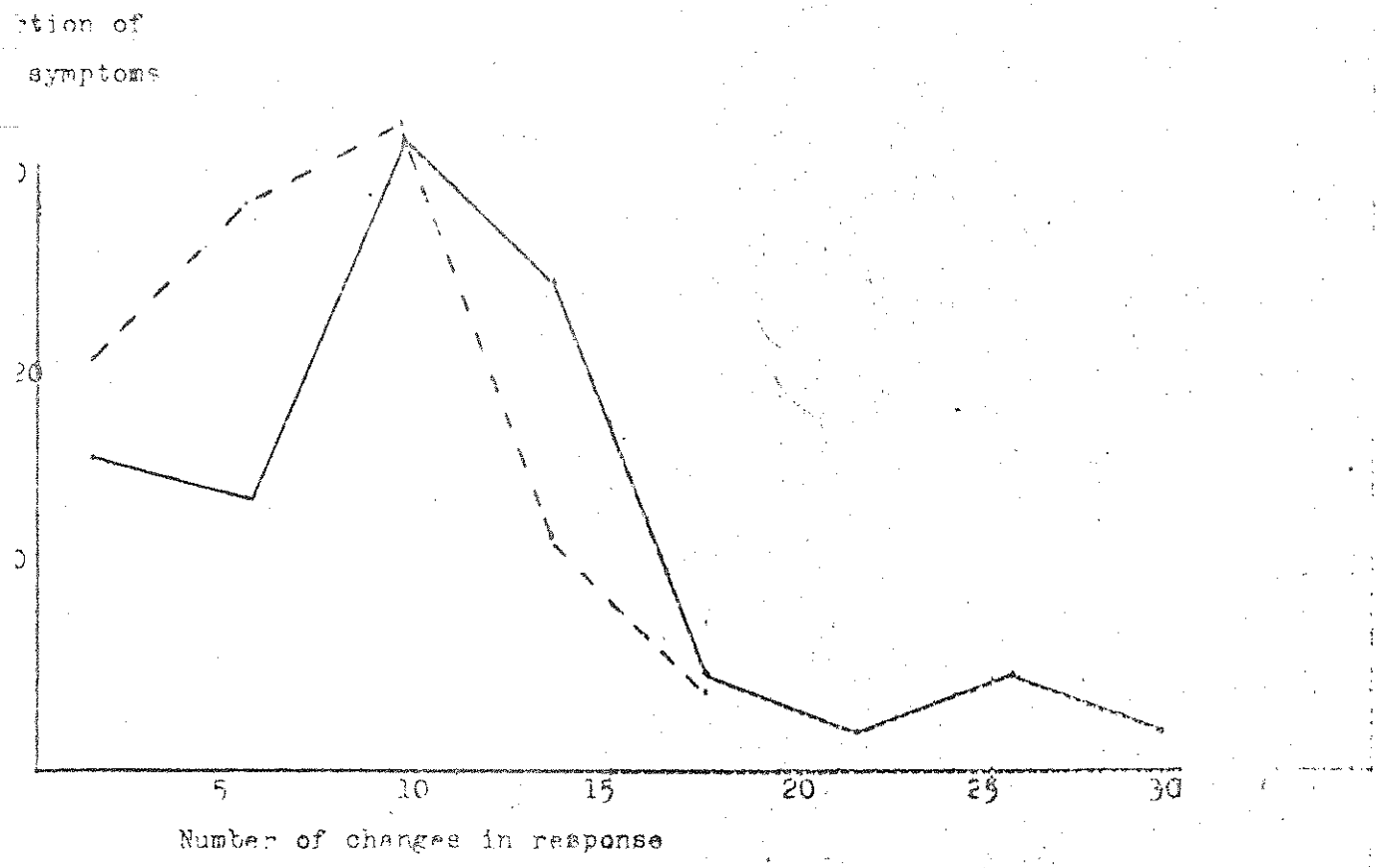
TABLE 18 : The proportion of control and experimental subjects showing total changes in response at equivalent time periods of Day 4 and Day 5.

Number of Symptoms	Proportion of Experimental Group	Proportion of Control Group
0 - 3	.16	.21
4 - 7	.14	.29
8 - 11	.32	.33
12 - 15	.25	.12
16 - 19	.05	.04
20 - 23	.02	
24 - 27	.05	
28 - 31	.02	

Frequency distributions of the total changes in response at equivalent time periods of Day 4 and Day 5, for the control and experimental groups can be seen in Figure 4 .

It is possible that the mean number of changes in response reported by the control group might have been smaller, had there not been a time lapse of three weeks between the administration of the first set of four questionnaires and the last. This lapse was unavoidable

FIGURE 4 : Distribution of the proportions of the total number of changes in response shown by the experimental and control group subjects at equivalent time periods of Day 4 and Day [illegible] in the experiment.



in the case of the experimental group, however, as the experimenter was not able to test all the subjects at the same time. The time lapse therefore had to be duplicated in the case of the control group.

The test retest measure of reliability of the placebo reaction measure was taken. The change in response reported by the experimental subjects from Day 4, pre-placebo to Day 1, placebo, was correlated with the change in response reported by the same subjects from Day 3, pre-placebo, to Day 2, placebo. The correlation of .45 ($p < .01$) was accepted as evidence that the placebo reaction measure used in this study was reliable. A measure of the total change in intensity of the reported responses for the experimental group was also taken. However, as the reliability of this measure was found to be only .10, it was dispensed with.

Hypothesis I can now be partially accepted, in view of the results that the experimental group of subjects showed more changes in reported symptoms after administration of placebo, than did the control group, to whom no placebo was given. However, the difference in reported intensity of symptoms, from the control to the experimental group, was not tested because of the unreliability of the measure.

As the writer has presented a valid and reliable measure of reaction to placebo, it is felt that the

remaining hypotheses can be tested. It must be noted however, that the approach of labelling subjects as "reactors" or "non-reactors" has been rejected. The typological approach can only be used when the distribution of scores of subjects reacting to placebo is a bi-modal one. Because of certain indications from previous experiments, the present study contained a central hypothesis, which was: "That there are identifiable placebo reactors and identifiable non-reactors. There will be more of the former among high anxious persons, and the reactors will be further differentiated in other behaviour characteristics, e.g. they will be more suggestible generally." It can be seen from Figure 4, that this is not the case in the present study. All experimental group subjects were affected in some measure by the administration of placebo, and there was no discernable dichotomy of response.

Jellinek (1946) was the first to introduce the terminology, despite the fact that his differentiation was actually based on degree and consistency of reaction rather than on an all-or-none basis. The use of the terms "reactor" and "non-reactor" was perpetuated, in spite of the lack of reported evidence that an actual dichotomy occurred. Lasagna et al., (1954) were the first to talk of the personalities of reactors and non-reactors. A tradition therefore seems to have

quickly arisen, that two such types of subjects may be easily statistically demarcated. While this attitude may appear to have a superficial clarity of approach, none of the studies reported have actually demonstrated that the use of the terms is statistically justified. Rather, there are indications, as in this study, that there is a differentiation in degree of reaction only. As the personality variables of introversion-extraversion are not dichotomously distributed in the population at large, so it may be reasonable to accept that placebo reactivity is also not dichotomously distributed, in so far as the concept may be compared with a personality variable.

This is not to assume that under different experimental conditions some subjects would not show a complete lack of response. However, this is to deal with the question of situational variables and their influence on the response to placebo as opposed to the question of the distribution of placebo reactivity as a trait. The present study was interested in studying only the relationship between the degree of reaction shown by the experimental group of subjects, and their scores on the various personality variables, and under these circumstances the use of the two dichotomised terms was thought unecessary.

The Results of Testing Hypothesis II.

Hypothesis II states "That the measurement of the total number of symptoms reported by subjects after the administration of placebo, is insufficient evidence of placebo reaction."

The use of response frequency was rejected in this study as a valid measure of placebo reaction measurement, despite its use by previous experimenters. It was pointed out that not only was a pre-test comparison of response frequency needed, before the administration of placebo, but the use of such a measure disguised the person who reacted to placebo by change in the type of symptom reported rather than significantly changing the total number of symptoms reported.

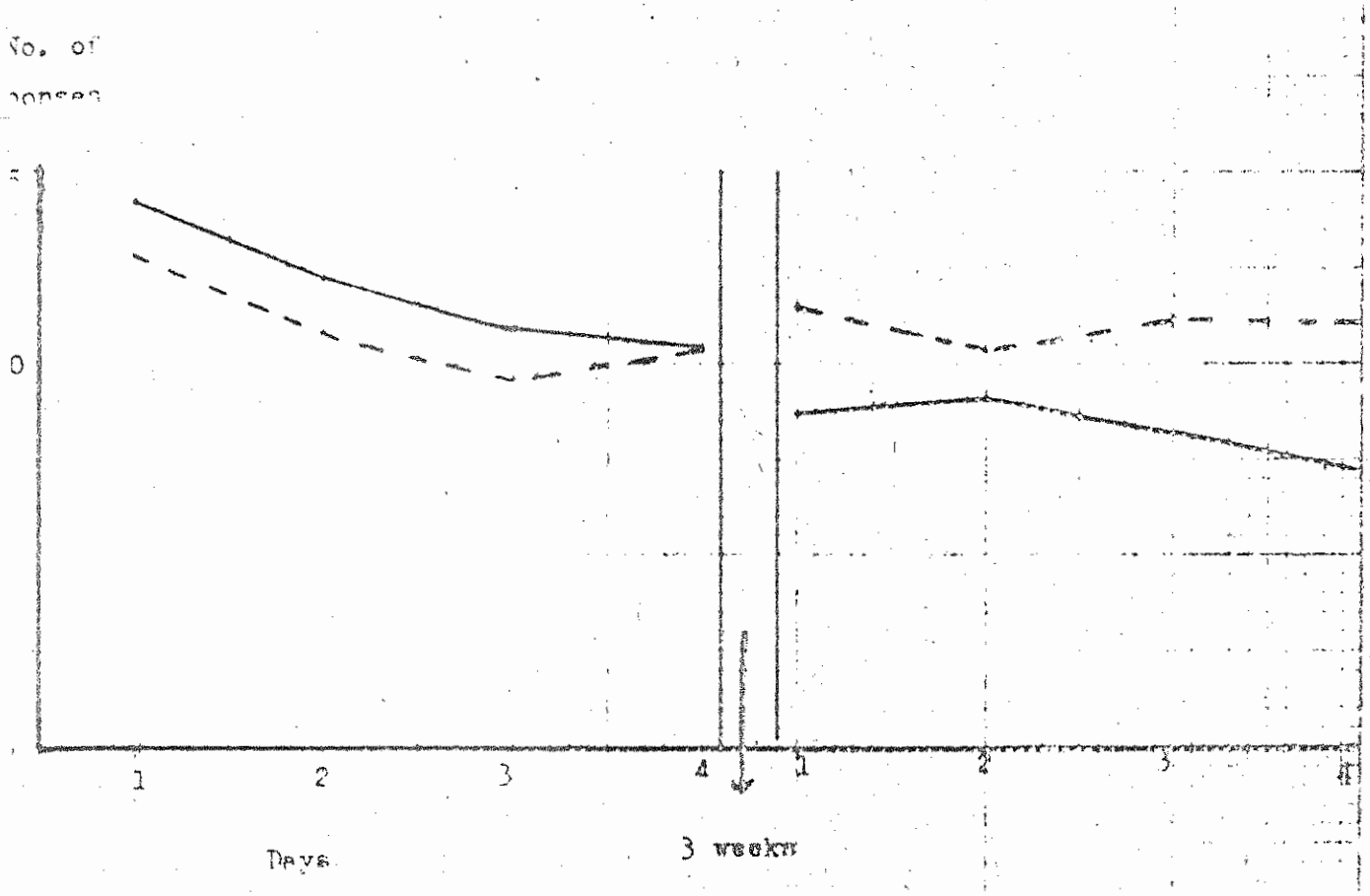
The mean number of symptoms reported each day for the experimental and control groups is presented in Table 19.

TABLE 19: The mean number of symptoms reported by the control group subjects and the experimental group subjects for 8 days respectively.

	Day 1	Day 2	Day 3	Day 4	Day 1	Day 2	Day 3	Day 4
Experimental	14.23	12.11	10.91	10.46	8.61	9.05	8.18	7.14
Control	12.75	10.79	9.58	10.42	11.50	10.42	11.17	11.12

It can be seen from Table 19 and from Figure 5 , that both the control and experimental group subjects show a steady decline in the number of symptoms reported for the first three days of the experiment, until a levelling off in response seems to occur. After the average time gap of three weeks per subject, and the administration of placebo to the experimental group, the pattern of response exhibited by the two groups changes. The spontaneous recovery shown by the control group would be expected in terms of renewed interest in the filling in of the questionnaire. However, the experimental group shows a significant decrease in the number of symptoms reported after the administration of placebo ($t = 2.48$, $p < .05$). It would appear that this is evidence that a placebo effect had occurred. The decrease in total symptoms reported, rather than an increase, greater than that shown by the control group, might be explained in terms of information gained by the experimenter in the course of the post-experimental enquiry interviews. When asked what type of drug they thought had been administered, twenty-three out of forty-four subjects claimed they thought it was a depressant of some type, or, more specifically, a tranquilliser. Of the remainder, two subjects believed they were receiving a stimulant, two thought they had taken both a stimulant and a depressant,

FIGURE 5 : The Mean Number of Responses to the Questionnaire shown by the 45 experimental subjects and the 24 control subjects for the 8 days of the experiment.



Experimental Group :

Control Group :

and the rest, (19, or 43 percent) had "no idea" as to what type of drug was administered. It was concluded that the attitude of the majority of subjects was a result of their greater familiarity with depressants. It was found that sixteen subjects had taken them at some time, and four had had experience in administering them. As the majority of experimental subjects thought they were receiving a depressant, the number of symptoms reported decreased as a result, and helped to produce the difference in the comparison of control group and experimental group means. Although this is evidence of a placebo reaction having taken place, it does not provide us with the additional and more subtle information needed. From the detailed analysis of the changes in the items reported previously, it may be seen that changes in the attitude of some of the subjects on being given the placebo also helped to reduce the total count of symptoms.

Those subjects who believed they were receiving a stimulant might well have shown an increase in the number of reported symptoms. Those who had no idea what type of drug they were administered could have shown either an increase or decrease in symptoms. And all subjects could have reported the same number of symptoms before placebo, as after, yet have reported different types of symptoms. The last point is well illustrated by Figure 6.

This shows that it was only the high anxious group of subjects which showed a decrease in the number of symptoms recorded. If, then, placebo reaction were defined only in terms of a total decrease in the number of symptoms reported, it would provide us with information about only one third of the subjects (i.e. the high anxious subjects.)

A validated method of measuring reaction to placebo has therefore been presented, which, it is felt, enables a more penetrating analysis of data than use of symptom frequency counts alone.

The Results of Testing Hypothesis III

Hypothesis III states "that those subjects with high anxiety scores will show a greater number of reactions to placebo, as defined by this study, than will those with low anxiety scores."

Two measures of anxiety were used: the Taylor Manifest Anxiety Scale and the second order factor, U.I. (L) and (Q) II from the 16PF. (Cattell, 1957.) By administering both tests, and measuring the correlation between them, the writer not only wished to add to the general knowledge of correlates of the T.M.A.S., but also to revoke, in the face of a positive correlation, the criticism of those who might support the use of the 16PF second order factor of anxiety as the selection criterion, rather than the T.M.A.S.

The correlation found between the two tests of anxiety was ·54 ($p < .01$). In view of this significant correlation, the choice of the T.M.A.S. was thought to be justified.

The correlation between the experimental subjects' placebo reaction scores and their T.M.A.S. results was ·35 ($.05 > p > .01$). This small but significant result was therefore accepted as an indication that anxiety, as measured by the T.M.A.S. is positively related to

placebo reaction (as defined by this study.) Because the placebo measure could have been more reliable as a measuring instrument, this result was corrected for attenuation, (using Taylor's retest reliability figures,) and the corrected correlation was ·70, suggesting that anxiety is an important factor in producing a reaction to the placebo.

The finding that anxiety shows a positive relationship to placebo reaction is in agreement with three previous studies, although their methods of investigating the relationship were criticised earlier. Lasagna et al., (1958) reported that reactors (defined by the method of response frequency) gave significantly more anxiety responses to the Rorschach than non-reactors. They then also ambiguously reported that reactors were more likely to have somatic symptoms during times of stress than non-reactors. This would seem the equivalent to saying that the reactors were anxious individuals. Gliedman et al., (1958) reported significantly more impressionistic diagnoses of anxiety amongst placebo reactors (defined by response frequency.) Abramson et al., found that questions eliciting the greatest percentage response in their questionnaire measuring placebo reaction, were those relating to anxiety. As was pointed out earlier, all these results are open to

some discussion, particularly in the use of qualitative measures of anxiety, such as the Rorschach and clinical opinion. In addition, Abramson et al., reported that reactors responded most frequently to those questionnaire items which were concerned with anxiety. This leaves some doubt as to whether the tendency was to respond to these items as a result of placebo administration, or because the tendency was for anxious subjects to respond to those items because they were anxious.

In the present study it was accepted that the tendency for high anxious subjects to report more symptoms could confound results, and this possibility was taken into account in the method of measurement used. Therefore, the positive correlation between anxiety and placebo reaction may serve as an interesting indication for further research.

THE RESULTS OF TESTING HYPOTHESIS IV

Hypothesis IV stated "That those experimental subjects labelled as high anxious will give more responses to the questionnaire used as a measuring instrument both in the pre-placebo and placebo condition, than will those experimental subjects labelled as low anxious."

The indications from previous studies was that perhaps high anxious subjects would give more positive responses to questionnaires while taking placebo, not because of the administration of placebo, but because they were highly anxious, and would answer such questions under normal, non-placebo conditions. In order to ascertain whether this was the case, high anxious subjects' total responses to the questionnaire would have to be measured under conditions of placebo administration, and then compared with their total responses given in a control, no placebo situation.

Table 20 shows the mean number of symptoms reported by the three Anxiety groups, over the eight days of pre-placebo and placebo conditions, and Figure 5 is a graphed distribution of symptoms reported by the three groups of subjects.

TABLE 20: The mean number of symptoms reported by the 45 experimental subjects, categorised as High, Medium and Low Anxious, under conditions of no placebo and placebo, for eight days.

	PRE-PLACEBO					PLACEBO				
	Day 1	Day 2	Day 3	Day 4	Total	Day 1	Day 2	Day 3	Day 4	Total
High	19.47	16.26	14.80	14.53		10.00	10.87	9.73	8.87	
Medium	12.20	10.67	10.13	9.53		9.33	10.47	9.13	7.07	
Low	11.40	9.27	8.00	7.33		6.73	6.00	5.93	5.80	
Total	14.23	12.11	10.91	10.46	47.11	8.61	9.05	8.18	7.14	33.96

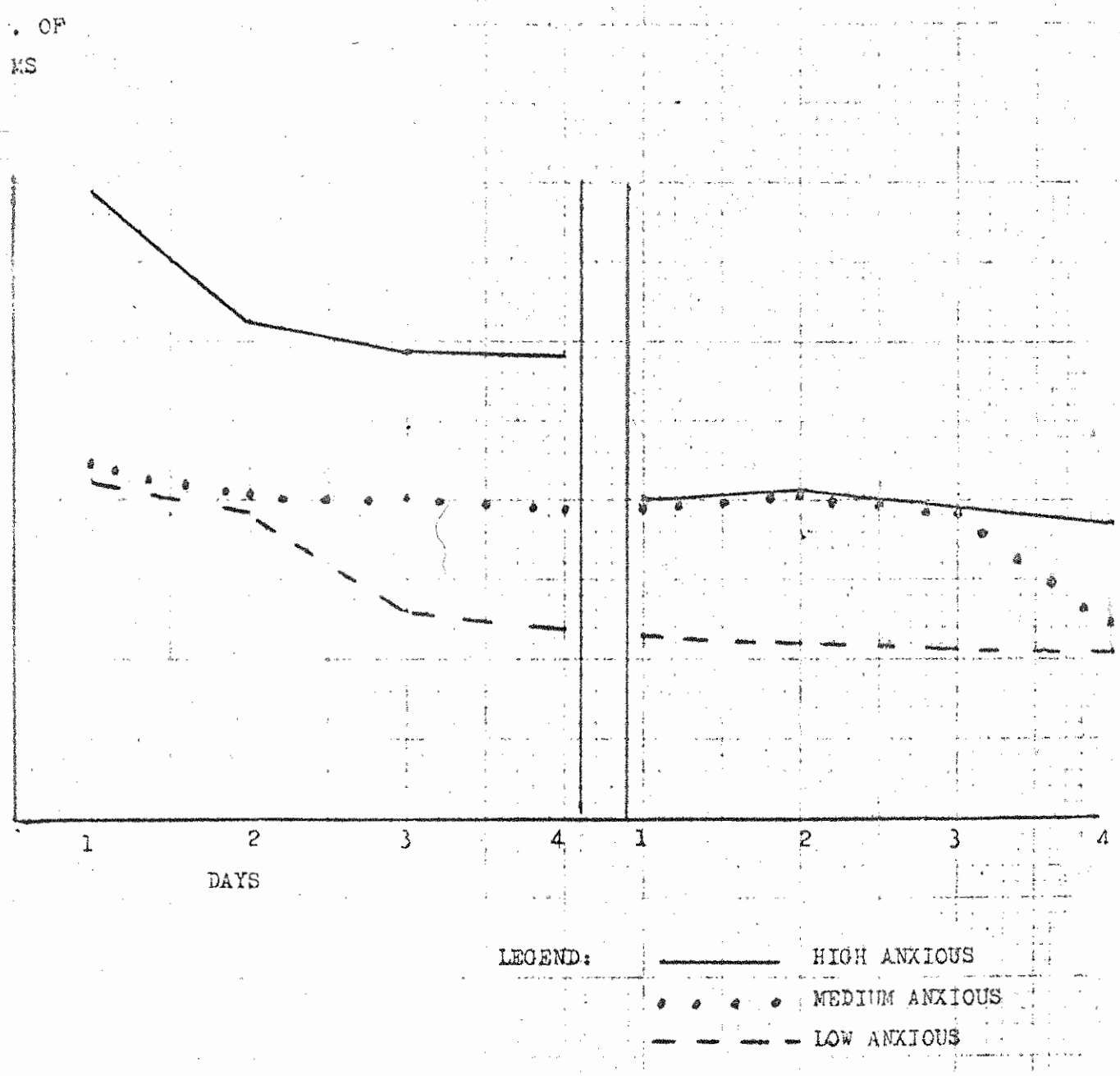
The t test for the Calculation of Necessary Differences (Lindquist, 1953, p.93) was used to test the difference between the means shown for the Anxiety groups in Table 20. From application of the formula,

$t \times \% \times s \frac{\sqrt{2}}{\sqrt{n}}$ 2.764 was accepted as the critical difference necessary to indicate a significant difference between the means of the high and low anxious subjects' scores at the .05 level of significance.

As the smallest difference between the means of the high and low anxious subjects, that for Day 4, placebo, was significant, (3.07, $p < .05$) it was accepted that the difference between the means on the other seven days was significant.

These results indicate that Hypothesis IV can be accepted, as it has been shown that high anxious subjects report significantly more symptoms than low anxious subjects, whether they are receiving placebo or not.

FIGURE 6: The mean number of symtoms reported by the 45 experimental subjects, categorised as High, Medium and low Anxious, under conditions of no placebo and placebo.



There would seem to be some indications here for future research in this field, where use is made of questionnaires to measure placebo reaction. It would appear that there should be awareness that high anxious subjects, if used in an experiment to study placebo reaction, will report more symptoms than low anxious subjects. A control situation, where there is measurement of symptoms reported without placebo, should be undertaken.

In addition, it would appear that to define placebo reaction in terms of the total number of symptoms reported, can be a misguided procedure. It is perhaps clear that high anxious subjects cannot be labelled as placebo reactors on the basis of the total number of symptoms they report being significantly larger than those reported by low anxious subjects. The relevant variable here is anxiety level, not the administration of placebo.

These results would also seem to have relevance to both drug studies and placebo studies. If high anxious

subjects will always report a greater number of symptoms, regardless of the experimental situation, then it is clear that no longer can random samples of subjects be used in drug studies, in particular, but each subject's score on the personality variable of anxiety must be known before any conclusions may be drawn. The type and frequency of symptoms reported in response to the administration of an active drug are important factors in any drug study. If high anxious subjects will report more symptoms under pre-drug and drug conditions, as indicated by the present study, then these individuals must be demarcated in an experimental sample, and their contribution to the total number of symptoms reported by the sample must be controlled for in the experimental design.

The type of symptom reported by subjects in an experiment to study the effects of an active drug is also important. The number of toxic symptoms, for example, that are reported after the administration of a drug, have a great deal of relevance. If the side effects of the drug are considered too toxic in comparison to its therapeutic efficacy, then it must be rejected. Similarly in placebo studies, it is of interest to note that some reactors report a large number of toxic reactions to the placebo. Previous

experimenters in this field have not attempted to find out whether these subjects also report more toxic symptoms under a pre-placebo condition. Nor did they attempt to differentiate those subjects who reported more toxic symptoms than non-toxic symptoms on the basis of personality variables.

As the present study has indicated that high anxious subjects report more symptoms than low anxious subjects, it was thought to be of additional interest to see if high anxious subjects also reported more toxic symptoms under the pre-placebo and placebo conditions, when compared to low anxious subjects. No hypothesis was offered earlier to test this, but it is considered, in the light of the results of the testing of Hypothesis IV, to be an additional observation of some interest.

Accordingly, the total number of toxic items in the questionnaire answered positively by each experimental subject under the pre-placebo and placebo condition was recorded. The total number of toxic symptoms reported by each subject for each of the eight days under the two conditions is reported in Appendix B. A list of the items in the questionnaire defined as toxic is shown in Appendix A.

Table 21 shows the mean number of toxic symptoms reported by the three Anxiety groups, for the two conditions.

TABLE 21: The total mean number of toxic symptoms reported by the 45 experimental subjects, categorised as high, medium and low anxious, under conditions of no placebo and placebo.

	PRE-PLACEBO	PLACEBO
High	47.6	28.47
Medium	27.00	26.93
Low	18.93	15.17

The t test for the Calculation of Necessary Differences was used to test the difference between the means shown for the Anxiety groups shown in Table 21. From application of the formula, 10.38 was accepted as the critical difference necessary to indicate a difference significant at the .05 level of significance between the means of the high and low anxious subjects.

The difference between the high and low anxious means for the pre-placebo condition was 28.67, and was significant ($p = < .05$). Similarly, the difference between the high and low anxious means (13.30) for the placebo condition was significant ($p = < .05$).

These results indicate that high anxious subjects tend to report significantly more toxic symptoms under normal conditions (i.e. pre-placebo control conditions)

and also when they are administered placebo, than do low anxious subjects.

It would seem, therefore, that those studies assessing the effects of either the administration of placebo or active drugs, should allow for the interaction of responses to placebo and/or active drugs, and the anxiety level of the subjects. In addition, if the total number of responses to a placebo or active drug is to be accepted as "a reaction," then these responses must be compared with responses measured before the placebo or drug is administered, and the anxiety levels of the experimental subjects clearly demarcated from the outset. Finally, the reporting of toxic symptoms as response to the administration of an active drug or placebo cannot be accepted as arising from the "effects" of either, unless the number of toxic symptoms reported by the same subjects under normal conditions is assessed, and account taken of the indications of the present study, that high anxious subjects will report more toxic symptoms than low anxious subjects under both the experimental and control conditions.

From further observation of the results in Table 20 and 21 it would appear that for the typical placebo study, where the measure of reaction is the total response frequency, high anxious subjects should not be used because of the inconsistency of their responding.

The Results of Testing Hypothesis V

Hypothesis V states "that those experimental subjects with high neuroticism scores, will show a greater number of reactions to placebo, as defined by this study, than those with low neuroticism scores."

The M.P.I. scores of neuroticism for the experimental subjects were correlated with their placebo reaction scores. The resulting correlation of ·25 was significant ($p < .05$) if a one-tail test is applied. It would appear that this degree of relationship between neuroticism as measured by the M.P.I., and reaction to placebo is only about that to be expected from the relationships between these two variables and the Taylor Scale scores. In fact the correlation between M.P.I. neuroticism and reaction to placebo falls to 0.03 if the influence of the Taylor scores is partialled out. This suggests that the clinical notion that neurotics were more prone to react to placebo could be true in so far as neurotics tend to be highly anxious.

Despite a "general feeling" by researchers (cf. Sainz et al., 1957) similar to that held about suggestibility, that neurotics were more prone to react to placebo, this study has not clearly supported the theory.

The Results of Testing Hypothesis VI

Hypothesis VI stated "that scores obtained by the experimental subjects in the measurement of primary suggestibility (as defined by Eysenck) will be positively related to their placebo reaction, as measured by the present study."

The Body Sway test and the test of Arm Bending suggestibility were used as a measure of the factor. The means and standard deviations for the two tests are shown in Table 22.

TABLE 22: Means and Standard Deviations for the tests of Primary Suggestibility given to the experimental subjects.

	Body Sway	Arm Bending
$\bar{X}$ movement in inches	7.73	1.32
S.D.	1.921	1.79

When the scores of the experimental subjects on these two tests of Primary Suggestibility were correlated with their placebo reaction scores, the Body Sway test was found to correlate -.01, and the Arm Bending test correlated .14 ($p > .10$). (The two tests correlated .57 with each other.)

It would appear obvious that no relationship can be shown to exist between Primary Suggestibility and placebo reaction, as measured by this study. Although this result may appear surprising in view of the relationship found in the present study between anxiety and reaction to placebo, and Eysenck's finding (1947, p.188) that Primary Suggestibility was correlated with anxious personality (i.e. dysthymia), it is in line with such findings as those of Gliedman et al., that Primary suggestibility as measured by the Body Sway Test, is not related to placebo reaction, as defined by their study. This agreement occurred despite the fact that in Gliedman's study the Body Sway Test was administered by a number of experimenters, despite some evidence that this can influence subjects' responses (Eysenck, 1943.) Also, the definition of placebo response given by Gliedman et al., was in terms of response frequency, rather than the method used by the present writer.

The Results of Testing Hypothesis VII

Hypothesis VII states "that scores obtained by the experimental subjects in the measurement of Evans' suggestibility Factor B, prestige authoritarianism, will be positively related to their reactions to placebo, as measured by the present study." The Ink Blot test was used to measure this Factor. The correlation of scores produced by the experimental subjects on this test, with their placebo reaction scores, was -.11, ($p > .10$).

The hypothesis must be rejected on the basis of this result. However, Evans (1961) wrote, in his interpretation of Factor B, "Perhaps it is not the nature of the stimulus situation, per se, which creates the set or expectancy that the present stimulus pattern will continue. The set or expectancy is accepted, not because of the nature of the stimulus situation, but as emanating from the authority or prestige value of the suggestor; this is provided that the stimulus does not differ sufficiently from the 'training' trials to the 'test' trials to negate the effect of the prestige suggestion by creating a situation beyond the credulity of the suggestee." (Evans, 1961, p.10.)

It would seem that in the present experimental situation, the subjects' knowledge that the experimenter was merely a graduate student in the Department of Psychology, may have affected their results on this test of suggestibility and its subsequent insignificant correlation with reaction to placebo. That is, the experimenter's position in the Department, as viewed by undergraduate students, would not have rated high in prestige value. It would therefore be of interest to study the results of a correlation between the Ink Blot test and placebo reaction, when subjects were tested in a situation, and by an experimenter, with a greater prestige rating; for example, by a resident medical officer in a hospital setting.

Results of the post-experimental enquiry interviews of the present experiment indicate that the experimental stimulus did not "create a situation beyond the credulity of the suggestee." These results may be seen in Table 23 which shows the percentage of subjects who reported certain impressions of the experimental situation. The fact that 63.6 percent of subjects reported that they were certain they were receiving an active drug would seem to indicate that the writer was reasonably successful in presenting the façade of an experimental situation which was accepted by the majority of subjects. This conclusion

is strengthened by the fact that only one subject expressed that she was convinced that the experimental situation was designed to measure responses to placebos, which were administered to all experimental subjects.

TABLE 23: The experimental subjects' impressions of the purpose of the experiment, as determined by post-experimental interview.

EXPERIMENTAL AIM	% OF SUBJECTS
That the study was to measure reaction to placebo	2.2
No idea	2.2
That the subjects were receiving partly active drug and partly placebo in a study measuring reactions to a drug	18.1
That the subjects were receiving only placebo as a control group in a study of an active drug	4.4
That the study was measuring reaction to a drug which the subjects were receiving	63.6
That the study was measuring reactions to a drug, and the subjects were in the control group, but not certain whether partly or completely receiving placebo	4.4
That the subjects were receiving placebo, but were not certain whether this was as part of a study of a drug or a placebo study	4.4

The Results of Testing Hypothesis VIII

Hypothesis VIII states "that scores obtained by the experimental subjects in the measurement of Evans' suggestibility Factor C, uncritical passivity or indirect learning, will be positively related to their reaction to placebo, as measured by the present study." The Heat Illusion test was used to measure this Factor. The correlation between scores on the Heat Illusion test and placebo reaction scores was -.22 (p .10). Although insignificant, this negative correlation approached the .05 level of significance. Because of this, further discussion might appear warranted.

Evans writes in his description of Factor C, "... it may be reasonable to postulate a sort of indirection, or uncritical acceptivity of the implied situation by the suggestee, as the basis of the factor. The suggestee accepts the occurrence of the stimulus uncritically, becomes indirectly conditioned to it, or indirectly 'learns' the suggested response. The test trials are tests of the uncritically accepted, or 'learned' idea." (Evans, 1961, p.11).

It would appear, then, on the basis of this interpretation of Factor C, and the small negative correlation between the measure of Factor C used in this study and placebo reaction, that the experimental subjects

did not entirely accept the presentation of the stimulus (placebo) uncritically. That this is so may be seen from Table 23, which shows that 31.3 percent of subjects reported that they thought that the aims of the experiment deviated in varying degrees from those aims expressed by the experimenter.

It will be remembered that the writer rejected Eysenck's assertion that the Ink Blot test and the Heat Illusion test loaded on a Factor he labelled Secondary Suggestibility, and accepted instead evidence submitted by Evans (1961) that the tests comprised the basis of two separate factors. As the correlation found in the present study, between the Heat Illusion test and the Ink Blot test was .05 ($p > .10$) it was felt that this result justified the rejection of Eysenck's Factor of 'Secondary Suggestibility.' If Eysenck's assertion of the existence of a Factor of Secondary Suggestibility were acceptable, then it would appear that the correlation between these two tests of suggestibility should be high and positive, for Eysenck claimed they both loaded on his factor, and were therefore measures of 'Secondary Suggestibility.'

It was pointed out in Section I that the majority of studies investigating placebo reaction accepted that suggestibility was an inherent part of, or the sole cause

of, reaction to placebo. For example, Abramson et al., (1955) wrote, "It seems that it was the ideationally oriented individuals rather than the primarily action-oriented individuals who demonstrated a greater amount of suggestibility, that is, a greater response to the placebo, in our experiments." (Abramson et al., 1955, p.381.) This was a statement typical of the untested assumption that placebo reaction and suggestibility were virtually inter-changeable concepts. Such work as that of Gliedman et al., which reported no relationship between the Body-Sway test and placebo reaction (as measured by response frequency) does not seem to have found general acceptance. Therefore, it would seem that the lack of correlation found between the factors of suggestibility and the reaction to placebo in the present study, is of some interest in view of the conflict of opinion in this area.

The Results of Testing Hypothesis IX

Hypothesis IX states "that those experimental subjects with low extraversion scores, as measured by the M.P.I., will show a greater number of reactions to placebo, as defined by this study, than will those with high extraversion scores."

The M.P.I. scores of extraversion for the forty-five experimental subjects were correlated with their scores of reaction to placebo. The resulting negative correlation of -.30 was significant ($.05 \quad p < .01$). Therefore Hypothesis IX was accepted. It would appear that introverted subjects, as measured by the M.P.I. are more prone to placebo reaction (as defined in this study) than are extraverts. Because the method used to measure placebo reaction could have been more reliable ($r=.4$)[2] the correlation between extraversion and placebo reaction was corrected for attenuation (using Eysenck's figures of retest reliability for the M.P.I. E scale), giving a value of -.51 which suggests that introversion is a factor to be taken into account in considering reaction to placebo.

No study has reported an investigation of the relationship between extraversion and reaction to placebo, neither did any post hoc analyses of relationships to

personality variables reveal that introverts were more prone to respond to placebo. This might be explained as due to the fact that no previous researchers used a measure of extraversion. Lasagna's description (1958) of reactors as "more dependent on outside stimulation than on their own mental processes" would seem a description of an extravert rather than the introvert. In their use of the Rorschach test, Lasagna et al., did not mention the reactors' scores on the M% variable, which Eysenck found (1956 b) to have the highest saturation on the introverted side, of a factor of extraversion.

In 1947 Eysenck reported a correlation between dysthymia and primary suggestibility. Later (1960) he suggested that primary suggestibility might be related to placebo reaction. The present study would confirm a relationship between introversion (dysthymia) and reaction to placebo, but not the relationship with primary suggestibility.

DISCUSSION OF THE RESULTS

This study was not an attempt to test the therapeutic efficacy of a placebo, but to observe the reaction to a placebo, defined as an inactive substance and represented as an active, (and in this case unnamed) drug. In this context, it would appear that the investigation of the two main aims of the experiment (encompassing the nine hypotheses) was successful.
Aim I: The attempt to find if any consistent type of reaction to placebo was elicited from an experimental group of forty-five subjects.

Fischer et al., (1956, p.510) point out that "the 'placebo reaction' is the physiological and psychological reaction to the administration and acceptance of the placebo." (our italics.) It is agreed that it is of fundamental importance that the subjects taking the placebo accept it in the manner in which it is presented, that is, as an active drug. From the results of the post-experimental enquiry interviews in the present study, it is clear that the majority of subjects (i.e. with the exception of three) believed that they were receiving an active drug. Once this is established, a reaction to placebo can then be investigated.

If a placebo "mobilises the expectancy" of the subjects to whom it is given (Frank, 1960), it is not

sufficient to investigate reaction to placebo in only a clinical or therapeutic context, and then generalise about types of reactions and reactors, as has been the case in previous investigations. Bearing this in mind, Lasagna et al., (1958) concluded of their experiment, "It must be remembered that this study was concerned only with the behaviour of placebo reactors to the subjective response of pain. We must wait for other studies to determine whether placebo reactors show the same characteristics for other subjective and objective responses." (p.778.)

The experimenter should not expect, necessarily, what has been called a 'positive' reaction from subjects (i.e. therapeutic efficacy or lessening of reported symptoms.) To define the direction of reaction to placebo is not only to restrict, and therefore to distort, the definition of a placebo reaction, but to ignore the possibility, of individual differences in reaction. Lasagna et al., (1958) for example, put forward the hypothesis that placebo reactors had a psychological make-up that predisposed them to anticipation of pain relief from any medication. This would appear a too restrictive approach to placebo reaction.

There would appear to be some constancy of the placebo effect in a wide variety of conditions (cf. Beecher, 1956) and this would suggest that a fundamental mechanism

in common is operating. In order to gain greater understanding of this process, it was the writer's thesis that reaction to placebo should be studied in as unstructured a situation as possible, and using a method of measurement of reaction to placebo flexible enough to take into account individual differences in reaction.

The following are some of the variables, in the present experiment, which could affect subjects' reactions to placebo.

i. The subjects' previous medications.
ii. The subjects' personal knowledge of the experimenter.
iii. The reputation of the experimenter.
iv. The community belief in recent achievements in medicine and pharmacology.
v. The relevant properties of the setting in which the experimenter operated.
vi. The experimenter's personality and behaviour and own expectations.

Because of individual interpretations and experience of these factors, it would be unwise to predict subjects' reactions to placebo in any one direction. Therefore the problem was to determine if a <u>change</u> in reaction occurred after the administration of a "drug." To determine if any apparent change was genuinely produced

by the introduction of placebo, or was an artifact of uncontrolled variables in the experimental situation, an experimental and control group were used. The experimental group's reactions to placebo was compared with its pre-placebo reactions, and the control group's reactions were measured for a similar time period, without the introduction of placebo.

Both the experimental and control group subjects reported responses to the questionnaire which progressively diminished for three days and then seemed to reach a steady level. This result would appear to have significance for both placebo studies and experiments in pharmacology. All subjects reported responses, or symptoms, accepted by researchers as indicative of changes brought about by active pharmacological agents or placebos, represented as active substances. It is clear, therefore, that no conclusions should be drawn about the symptomatic effects of either drug or placebo, without reference to the normal 'base line' of symptoms reported by individuals in a control situation. Reactions to drugs or placebos can therefore be said to contain a certain percentage of symptoms which an individual would report normally, without additional stimulus in this way. It may be argued that undergraduates would be more careful about filling in the questionnaire than non-University subjects.

While it is accepted that this may be so, the writer doubts if it would cause a significant difference in the number of symptoms reported by University and non-University subjects in this manner.

The finding that subjects report a varied number of symptoms without apparent legitimate stimulation would explain many puzzling results reported in the literature. It would explain, for example, why active drugs appeared successful at the time of a clinical trial, and yet, after more prolonged use, exhibited no real effect. It would also explain the Glaser and Whittow results (1953.) They wrote: "No satisfactory explanation is available for the high incidence of symptoms in initial tests...." (p.44p) after reactions to placebo, reported on a questionnaire, had diminished steadily after a period of days. It is perhaps clear from the results of the present study, that a similar symptom frequency will be elicited from subjects without placebo, and if placebo reaction is to be studied in terms of total response frequency, it must be compared to response frequencies reported before placebo is introduced.

Abramson et al., wrote, in their 1955 study, "Subjects who gave positive responses under placebo, did so under actual LSD-25." (Abramson et al., 1955, p.381).

This is in essential agreement with results reported by Lasagna et al., 1954.

It is suggested that there might be a tendency for some subjects (and the present study indicates that these would be high anxious subjects) not only to react (i.e. report symptoms) under these circumstances, but to respond in this manner without what would appear legitimate stimulation. This would explain the high correlations found between reactors to drugs and reactors to placebo, where reaction was accepted as total response frequency.

Experimental procedures, such as the filling in of questionnaires, or the taking of capsules, can give rise to apparent responses in human subjects according to Glaser et al., 1953. The present study would confirm this. It seems, then, the responses reported by subjects after the introduction of an experimental variable, must be compared to the responses recorded prior to this event if any conclusions can safely be drawn from pharmacological or placebo studies.

In the present study, while a pre-placebo and placebo measure of response frequency demonstrated that a placebo reaction had occurred, it was rejected as the most useful method of measurement. The method of measuring individual total change in response to items of the questionnaire was introduced as a valid and reliable measure. In this way

each subject was assigned a placebo reaction score. It was found that subjects showed a significantly reliable reaction to placebo (retest r= .45). No rigid dichotomy was found between placebo 'reactors' and placebo 'non-reactors', only varying degrees of response. However, any subject who gained a placebo score which was less than the mean number of changes in response reported by the control group, could only be labelled a chance reactor, and our concern in this experiment was the study of consistent reactors.

It is claimed that the method of measuring placebo reaction as total frequency of response change, overcomes the problem found by some workers in defining consistency of reaction. Some experimenters, such as Wolf et al., (1957) reported marked inconsistency of placebo reaction as shown by their subjects, which led them to reject the concept of a placebo reactor. However, they restricted 'reaction' to a directional measure. Any subject who reported a 'positive' effect would be labelled a reactor (in their study, this meant an inhibition of response) and a subject who produced a 'negative' effect or no effect, was labelled a non reactor. Thus, any subject who changed the direction of his reaction was labelled inconsistent.

The present writer would maintain that this is unnecessary, and, in reality, as a method of classification, labels a placebo reactor as an inconsistent or unreliable reactor, when it is only the type of reaction that varies.

It was admitted in the present study that the questionnaire used as a measuring instrument could well be a limited instrument in assessing reaction to placebo. However, from the analysis of total changes in response reported by the experimental subjects to the individual items of the questionnaire, it was found that no useful scale of items, out of a range of fifty-three possible items, could be developed for finding placebo reactors. That is, it was established that no typical placebo reaction existed, independent of the type of "drug" being investigated, although the present experimental design was such that this typical reaction would be clearly demonstrated if it was exhibited by enough subjects. However, the placebo reactors did not report changes in a consistent set of items, but varied in the reactions they showed.

It is suggested that a profitable approach to further research in this area would be to duplicate

the experimental design used in the present study but to inform the subjects that they were receiving a specified drug, i.e. a stimulant or depressant. In this way a consistent pattern of symptoms might be reported by those subjects who were reactors, which corresponded to the type of "drug" being administered, in comparison to their pre-placebo symptoms. The measure of reaction would be of necessity, change in response.

Aim II: An attempt to find if any particular personality type produces reaction to placebo.

The majority of investigators studying reaction to placebo have suspected or observed, mainly by subjective clinical methods, that anxiety was related to reaction to placebo. (cf. Beecher, 1956; Lasagna et al., 1954; Tibbetts et al., 1956; Abramson et al., 1955; Gliedman et al., 1958). However, this subjective or clinical 'feeling' was always tempered by the additional suspicion that an anxiety-provoking situation was more relevant than the personality trait of anxiety. The two variables were never demarcated nor their differential effects tested in an experimental situation. The main problem, therefore, confronting all experimenters, was whether placebo reaction was a function of individual differences, or of situational conditions such as stress, or suggestion.

The present experimental design was an attempt to distinguish anxiety as a personality variable, from an anxiety producing situation, when studying the effect produced by the introduction of placebo. It was seen from the post-experimental enquiry interviews and the lessening of cooperation and enthusiasm as measured by items 48, 49 and 52 of the questionnaire, that the subjects found the situation anxiety-producing. However,

it was the high anxious group of subjects which was most significantly affected by the introduction of the placebo. If the reaction to placebo had been a function solely of the anxiety-provoking situation, then the low anxious subjects would have reacted to the placebo in a similar manner to the high anxious. It can therefore be assumed, that in the situation studied in the present experiment, reaction to placebo was related to individual differences rather than to the experimental situation.

Anxiety, as measured by the T.M.A.S. (which correlated ·54 with the 16PF second order factor of anxiety) was found to have a significant correlation (·35) with reaction to placebo, in this study. The use of a more objective measuring instrument of anxiety lends support to the conclusions of such as Gliedman et al., (1958) who reported significantly more clinical diagnoses of anxiety amongst those subjects labelled as reactors. This correlation between anxiety and placebo reaction, if accepted as a general indication that such a relationship would still exist if subjects of both sexes were tested by different experimenters in different situations at different times, provides a useful explanation of many findings reported in the literature.

Abramson et al., (1955) reported, for example, that the questions eliciting the greatest percentage response from subjects to whom placebo had been given, were those relating to anxiety. In view of the present results, it could be suggested that this was because those subjects who responded in such a way, did so because they were normally anxious, independently of the experimental situation. Lasagna et al., (1958) reported that 'reactors' were more likely to have somatic symptoms during times of stress, than 'non-reactors.' Once again it might be concluded that this was because those subjects who showed reaction to placebo were anxious subjects, and presented a history of somatic symptoms regardless of situations. Similarly, Wolf et al., (1954), showed how placebos could cause extensive "toxic" reactions. They used anxious, tense patients, and were surprised at the major toxic reactions from patients on placebo as well as mephenesin. The results of the present study indicate that this finding is to be expected. Those subjects who were categorised as high anxious reported significantly more toxic symptoms in both the pre-placebo and placebo conditions than did the low anxious subjects. Gliedman et al., (1958) suggested that the presence of toxic reactions to placebo was due either to the anxiety of the subject or to the

presence of a doctor, for example, as an anxiety-producing figure. The results of the present study would seem to demonstrate that an anxiety-producing figure is not necessary to produce these reactions. Not only did the high anxious subjects report such symptoms without the presence of an anxiety-producing figure, but when the experimenter was present during the administration of placebo, it could hardly be said that the social image of a graduate student was such as to cause anxiety.

The smaller, yet significant relationship of introversion, (as measured by the M.P.I.), to placebo reaction ($r = -.30$, with extraversion) is consistent, when taken into account with the correlation between anxiety and placebo reaction, and between the T.M.A.S. and M.P.I. extraversion ($r = -.30$, Eysenck, 1959) with Eysenck's description (1957) of the introverted neurotic, or dysthymic, as characterised by "anxiety, reactive depression, and/or obsession compulsion features." (Eysenck, 1957, p.26). It is suggested that subjects classified as prone to anxiety, depression and neurotic introverted tendencies, react to placebo in the sense that such reactions are overt manifestations of anxiety. Whether the tendency is to improve or feel worse after taking placebo, anxious subjects appear to exhibit or express such reactions,

while low anxious subjects do not show such a marked tendency.

In 1954, after investigating the literature, Leslie advanced the following definition of placebo: "A placebo is a medicine or preparation which has no inherent pertinent pharmacologic activity, but which is effective only by virtue of the factor of suggestion attendant upon its administration." (p.855.) This definition is typical of an acceptance, without any experimental evidence, that suggestion was the relevant situational or personality variable affecting reaction to placebo. The writer rejects the concept of there being suggestible situations; there would appear to be only suggestible subjects able to be influenced by certain situations. The present study explored the relationship between reaction to placebo, and factors of suggestibility as personality variables, and found no significant relationship. On the basis of these results, and in view of the lack of previous experimental evidence to confirm this relationship, despite frequent attempts, it is thought that a suggestibility theory approach to placebo reaction is outmoded. Alternatively, a tentative explanation of the results of the present study might be given in terms of learning theory.

The initial responses to the pre-placebo questionnaire situation by the experimental and control groups may be regarded as the result of generalisation from other learning situations, (the differences in response frequency occurring as the result of individual differences in personality variables) and the diminution of responses to this situation, on repetition, as the result of lack of reinforcement. The increase in responses by the control group, after an average time lapse of three weeks, was the result of spontaneous recovery. The significant decrease in responses shown by the experimental group was the result of the administration of placebo at this point. The decrease in symptoms may have been the result of the majority of subjects who labelled the placebo interpreting it as a depressant, and therefore showing response inhibition, rather than producing responses. If the above elementary interpretation in terms of learning theory is tenable, there is at once a hypothetical link with personality theory. According to Eysenck's (1955) theory concerning the basis of differences between introverts (and dysthymics) and extraverts (and hysterics) it would follow that the introverts would tend to acquire placebo responses more readily and to lose them less readily than the extravert. An alternative theory,

associated with Spence and his co-workers, relates anxiety to ease of conditioning. Either theory is compatible with the present data.

It is recognised that generalisations from the results of the present experimental sample, are, of necessity limited. Further research is necessary to duplicate results, not only with a similar sample, but with widely varied samples in a number of situations and using tests which purport to measure the same variables as the M.P.I. and the T.M.A.S. It would appear, however, that the results reported may serve as indicators for future study in this field.

CONCLUSIONS

Clinical pharmacological research must take account of the reactions of subjects to placebos, if such research is to be valid and if the results of such investigations are to extend the knowledge gained from more easily controlled experiments performed on animals and isolated tissues.

The importance of the placebo effect as a methodological problem has already been outlined. It must be appreciated that the placebo effect can be one of the reasons for failure to recognise a useful drug in a therapeutic trial. In addition, although placebo reactions may usually appear to enhance the drug effect, they may also subtract from it.

The significance of placebo reactions for psychiatry and clinical psychology is considerable. A more critical attitude is needed toward novel physical treatments. Some of these may prove in time to have almost specific properties, but the majority are likely to prove placebos, producing temporary improvement in about 40-70 percent of patients. The placebo effect must also be allowed for in assessing the results of psychotherapy. Certainly, recognition of the mode of action of a treatment is vital for real advance.

Without this knowledge, unnecessarily complex and even hazardous treatment may continue to be used and the results of treatment may mislead physiologists, psychologists and pharmacologists in developing their theories.

It is essential for a valid clinical test situation that the groups of subjects should be identical, except for the manner in which they are treated, whether they receive a placebo or an active drug. Identical groups can usually be obtained by relying on the statistical phenomenon that if two samples are drawn at random from a large population, the two samples will be statistically identical. In practice this involves assigning drugs and doses to the various subjects in a "chance" or random order that is independent of the experimenter's control or wishes.

However, the indications of the results of the present study are that the identical groups of subjects used in such clinical tests be matched on the personality variables of anxiety as measured by the T.M.A.S. or 16PF, and introversion, as measured by the M.P.I., before they are allocated to the placebo or drug groupings. In addition, if a symptom count is to be used as an indication of the effect of the drug, a control measure must be used. That is, the symptoms typical to the individual subjects must be recorded and

compared with the symptoms produced or alleviated by the drug being examined. The employment of single doses of placebo to "label" subjects as "reactors" therefore seems at best only a partial solution to the problem. Preliminary investigations must be made on a population which is to serve as a source of material for drug trials, and the anxious subjects demarcated. By studying the reactions of the high anxious subjects as compared to the low anxious subjects, it can be decided how much attention is to be devoted to the phenomenon occurring. It appears reasonable to assume that the higher the number of anxious subjects, the higher the number of placebo responses, and the greater the dilution of the desired data, and the more important the screening of subjects.

No predictions can be made from the results of the present study as to the health-promoting factors involved in a therapeutic context. While it might be predicted that highly anxious subjects would react to a placebo in a therapeutic situation, as the present study was not concerned with the clinical efficacy of a placebo, it could not be suggested that they would necessarily show improvement. The present writer was not concerned with predicting the direction of reaction to the placebo, but only in observing whether a reaction

did occur. It was found, however, that the high anxious subjects reported more toxic symptoms, both with and without placebo. But it could not be stated that high anxious subjects would tend to report more toxic symptoms in a therapeutic situation, because of the nature of the present experimental design. As the "drug" administered to the subjects was unnamed in order to eliminate expectancies associated with a specific drug or a specific clinical situation, and thus allowing more generalisations to be made about the nature of the reaction, it was open to individual interpretation as to whether it should have therapeutic potential or not. However, it could be suggested that before an active drug be discarded because of what would appear to be excessive toxic symptoms accruing to its administration, the high anxious subjects in the test population be demarcated, for the present study would suggest that the frequency of their reported toxic symptoms is significantly in excess of those reported by other anxiety groups, without the administration of any experimental agent.

It is recognised that generalisations from the results of administering placebo to a group of women undergraduates whose degree of anxiety was defined by two measures, may be limited. However, it is with

some confidence that the writer would assert that a placebo reaction did occur, and was measured, in this study. The finding that the personality variable of anxiety showed the most significant degree of relationship to the tendency to react to the placebo is in agreement with trends shown by previous researchers. It is maintained, however, that the present results may be accepted with some confidence, because of the additional means of control and the more precise application of experimental design, used to establish this relationship.

Placebo effects are probably the most relied upon aspects of pharmacotherapy today, however unintentional this may be on the part of the physician. The daily flood of samples and advertisements which flows over the desk of every medical practictioner is proof enough. Only a fraction of these materials has been rigorously tested and shown to have any kind of worthwhile pharmacodynamic effects. It is therefore concluded that placebo testing is essential to the validity of any clinical trial in which the subjective response of the subject or the subjective

impression of the tester is the criterion of the drug effect. The greater the psychological component in the patient's condition and the greater the influence of the patient's psychological state on his symptoms and physical signs, the greater is the necessity for placebo controls in the clinical trial of a therapeutic agent.

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APPENDIX A

A copy of the Taylor Manifest Anxiety Scale, as presented to the subjects.

THE AUSTRALIAN NATIONAL UNIVERSITY

DEPARTMENT OF PSYCHOLOGY

BIOGRAPHICAL INVENTORY FOR TEACHING PURPOSES

Do not spend too long on any one question.

1.	I do not tire quickly.	TRUE	FALSE
2.	I am often sick in my stomach.	TRUE	FALSE
3.	I am about as nervous as other people.	TRUE	FALSE
4.	I have very few headaches.	TRUE	FALSE
5.	I work under a great deal of strain.	TRUE	FALSE
6.	I cannot keep my mind on one thing.	TRUE	FALSE
7.	I worry over money and business.	TRUE	FALSE
8.	I frequently notice my hand shakes when I try to do something.	TRUE	FALSE
9.	I blush as often as others do.	TRUE	FALSE
10.	I have diarrhoea once a month or more.	TRUE	FALSE
11.	I worry quite a bit over possible troubles.	TRUE	FALSE
12.	I practically never blush.	TRUE	FALSE
13.	I am often afraid that I am going to blush.	TRUE	FALSE
14.	I have nightmares every few nights.	TRUE	FALSE
15.	My hands and feet are usually warm enough.	TRUE	FALSE
16.	I sweat very easily even on cool days.	TRUE	FALSE
17.	When embarrassed I often break out in a sweat which is very annoying.	TRUE	FALSE

18.	I do not often notice my heart pounding and I am seldom short of breath.	TRUE	FALSE
19.	I feel hungry almost all the time.	TRUE	FALSE
20.	Often my bowels don't move for several days at a time.	TRUE	FALSE
21.	I have a great deal of stomach trouble.	TRUE	FALSE
22.	At times I lose sleep over worry.	TRUE	FALSE
23.	My sleep is restless and disturbed.	TRUE	FALSE
24.	I often dream about things I don't like to tell other people.	TRUE	FALSE
25.	I am easily embarrassed.	TRUE	FALSE
26.	My feelings are hurt easier than most people's.	TRUE	FALSE
27.	I often find myself worrying about something.	TRUE	FALSE
28.	I wish I could be as happy as others.	TRUE	FALSE
29.	I am usually calm and not easily upset.	TRUE	FALSE
30.	I cry easily.	TRUE	FALSE
31.	I feel anxious about someone or something almost all of the time.	TRUE	FALSE
32.	I am happy most of the time.	TRUE	FALSE
33.	It makes me nervous to have to wait.	TRUE	FALSE
34.	At times I am so restless that I cannot sit in a chair for very long.	TRUE	FALSE
35.	Sometimes I become so excited that I find it hard to get to sleep.	TRUE	FALSE
36.	I have often felt that I faced so many difficulties I could not overcome them.	TRUE	FALSE

37.	At times I have been worried beyond reason about something that did not matter.	TRUE	FALSE
38.	I do not have as many fears as my friends.	TRUE	FALSE
39.	I have been afraid of things or people that I know could not hurt me.	TRUE	FALSE
40.	I certainly feel useless at times.	TRUE	FALSE
41.	I find it hard to keep my mind on a task or job.	TRUE	FALSE
42.	I am more self-conscious than most people.	TRUE	FALSE
43.	I am the kind of person who takes things hard.	TRUE	FALSE
44.	I am a very nervous person.	TRUE	FALSE
45.	Life is often a strain for me.	TRUE	FALSE
46.	At times I think I am no good at all.	TRUE	FALSE
47.	I am not at all confident of myself.	TRUE	FALSE
48.	At times I feel I am going to crack up.	TRUE	FALSE
49.	I don't like to face a difficulty or make an important decision.	TRUE	FALSE
50.	I am very confident of myself.	TRUE	FALSE

The items of the questionnaire used to measure the number of 'toxic' symptoms reported by the 45 experimental subjects. ✱

1. Headaches
2. Pains in the heart or chest
3. Heart pounding or racing
4. Trouble getting your breath
5. Constipation
6. Nausea or upset stomach
7. Loose bowel movements
8. Twitching of the face or body
9. Faintness or dizziness
10. Hot or cold spells
11. Itching or hives
12. Frequent urination
13. Pains in the lower part of your back
14. Difficulty in swallowing
15. Skin eruptions or rashes
16. Soreness of your muscles
17. Nervousness and shakiness under pressure
18. Difficulty in falling asleep or staying asleep
19. Moistness of your palms
21. Drowsiness or fatigue
22. Difficulty in focusing your eyes
23. Ringing or buzzing in your eardrums
24. Increased thirst
26. Sensation of heaviness in your head or limbs
28. Bad dreams
29. Feeling blue
30. Being easily moved to tears

✱ It must be noted that many of these symptoms would be regarded as 'normal', in everyday circumstances. However, they are accepted by many experimenters as 'toxic' when manifested after drug or placebo administration.

31. An uncontrollable need to repeat the same actions e.g. counting, touching etc.
32. Unusual fears.
33. Objectionable thoughts or impulses which keep pushing themselves into your mind.
34. Your 'feelings' being easily hurt.
35. Feeling that people were watching or talking about you.
36. Generally preferring to be alone.
37. Feeling lomely.
38. Feeling easily annoyed or irritated.
39. Feeling compelled to ask others what you should do.
40. Severe temper outbursts.
41. Feeling critical of others.
42. Frequently took alcohol or medicine to make you feel better.
43. Difficulty in speaking when excited.
44. Feeling unaccountably nervous.
45. Feeling your mind was slow and sluggish.
46. Feeling indifference or lack of concern.
50. A snese of restlessness.
51. Feeling confused and unreal.
53. Feeling inattentive and ineffective.

Sample Post-Experimental
Enquiry Interview

Subject No.8

Experimenter: Now Bridget, you remember the first time I saw you .... the first session.... I told you what the purpose of the experiment was. Right? Now, at any time during those four days did you have any ideas over and above what I said or in contradiction to what I said .... what the experiment might be about?

Subject: No. I don't think so.

Experimenter: In other words you accepted at face value what I said - that is, that I had you on an active drug for four days.

Subject: Yes.

Experimenter: You didn't doubt that at any time during those four days?

Subject: No.

Experimenter: Rightho. Now have you got any ideas as to what my aim might have been in this study?

Subject: What do you mean by that?

Experimenter: Well.... an hypothesis, or aim - what I was looking for.

Subject: To see how well a drug reacted when people didn't know what they were taking them for.

Experimenter: Uhuh. I see. And what about results? What are the results you think I'll get out of it?

Subject: .... I don't know. Some people seem to have different reactions.

Experimenter: Uhuh. Another thing Bridget - did it worry you at all that people were having different reactions to you, for example? How did you explain it to yourself that some people were reacting differently?

Subject: I think that different people react in different ways.

Experimenter: Uhuh.

Subject: I heard they had some results ....

Experimenter: Uhuh. Well, how do you think you went in the experiment - in other words, how your reactions affected the experiment as a whole?

Subject: I don't know .... I always get depressed for no reason. It might not have been the drug.

Experimenter: Uhuh. Bridget, would you like to hazard a guess as to what sort of drug it might have been?

Subject: I thought one of them might have been a pep drug.

Experimenter: Uhuh. That's a stimulant.

Subject: Mmm.

Experimenter: Why do you say one of them?

Subject: Because it was only once that I felt .... sort of gay afterwards.

Experimenter: Uhuh. You think I might have mixed the drugs?

Subject: I think some of them didn't have any reaction at all ....

Experimenter: Uhuh.

Subject: .... when I took them.

Experimenter: So because on one or two days you didn't get any reaction do you think you were on a different type of drug or no drug at all.

Subject: I must have been on no drug at all.

Experimenter: I see. No .... that's a .... what we call a placebo .... a drug that has no effect - or, you know, it's made up to look like one. Now would you like to pinpoint those two days?

Subject: The last one.

Experimenter: The last one. Now what do you think about that Bridget? Why do you think I would have had you on placebo?

Subject: To see if I had any reaction when there wasn't necessarily a cause for it.

Experimenter: Uhuh. I see. A sort of control measure. Now do you think I had everyone on this mixture of drug and placebo?

Subject: I don't know.

Experimenter: But you think you were on such a mixture.

Subject: I just know the drug didn't particularly have any reaction on me.

Experimenter: Uhuh. So that would you be prepared to say pretty decisively that you were on placebo, or that you were on a different drug, or the drug didn't have any reaction on those days?

Subject: I think it didn't have much reaction on those days.

Experimenter: Uhuh. So that you're not sure that you were on placebo or just that the drug didn't have any reaction.

Subject: Mmm.

Experimenter: But you think there was a possibility you could have been on placebo.

Subject: Mmm.

Experimenter: Well why do you think I would .... It didn't strike you as odd?.... Now did you come into the experimental situation expecting that?

Subject: No.

Experimenter: You didn't. You're doing some science subjects aren't you? Aren't you doing Zoology?

Subject: No.

Experimenter: Oh.

Subject: I do geography.

Experimenter: Just geography. Do you know anything very much about experimental control and experimental design?

Subject: Well particularly with psychological drugs you expect to see if there's any reaction.

Experimenter: So you practically expected such a control. It didn't bother you at all. You accepted this as a control measure.

Subject: Mmm.

Experimenter: And you thought it was particularly on the last day ....

Subject: Yes.

Experimenter: .... that you got a placebo, if it was. Right. Bridget, what sort of experience have you had with drugs, up to this point? By drugs I mean anything from aspirin upwards.

Subject: None. I've taken Veganin.

Experimenter: Mmm. Weren't you on hormone extract of some sort....?

Subject: The doctor had given me some pep pills.

Experimenter: So you have taken some stimulants. They were for pre-menstrual depression?

Subject: Uhuh.

Experimenter: I see.

Methods of Scoring

The Suggestibility Tests

The Body Sway Test.

Instructions:

1) Static Ataxia

"I want you to stand here, as you do ordinarily, but with your eyes closed."

2) Body Sway

"Now, keeping your eyes closed, you are swaying forward .... swaying further and further forward .... further forward .... your whole body is moving forward.... swaying further forward...."

Static Ataxia was measured by attaching a cord to the subject, and body displacement was recorded by maximum sway forward or backward. Duration of the test was 30 seconds.

Body sway was measured by maximum sway forwards or backwards with a correction for static ataxia.

The duration of the test was 60 seconds.

The Arm Bending Test (Passive)

Instructions:

"Your right arm is tingling, tingling as if it were about to move. Your right arm is beginning to move.... you can feel it moving....further and further, round over your body. Feel it moving, further and further, round over your body...."

Similar instructions were continued for about 2 minutes, or until maximum bend occurred if in less than 2 minutes.

Scoring

Maximum Fast	Maximum Slow	Moderately Fast	Moderately Slow	Little Fast	Little Slow	No Response
6	5	4	3	2	1	0

Scoring Method used to Measure Change in Degree of Response as indicated by the items of the Questionnaire

Question I (Headaches) may be used as a typical example.

Rating	Score
Have not had this symptom	0
Slightly distressed	1
Moderately distressed	2
Severely distressed	3

Each subject's score on each item was noted for Day 4, pre-placebo, and Day 1, placebo. If there had been a change in rating of the degree of having the symptom it was scored + for an increase (i.e. a change of from 1 to 3) and - for a decrease (i.e. a change of 3 to 1). No change was not taken into account for the purposes of computation in the McNemar Test of Significance of Change.

APPENDIX B

Raw Scores for the 45 Subjects Participating in the Experiment for the four Personality Variables, M.P.I. Extraversion, M.P.I. Neuroticism, Taylor Anxiety and 16PF Anxiety

SUBJECTS' NUMBER	M.P.I. EXTRAV.	M.P.I. NEUROT.	TAYLOR ANXIETY	16PF ANXIETY
3	36	14	9	3.7
5	6	11	22	5.8
10	29	25	19	6.6
11	39	24	6	5.2
12	16	48	37	8.7
13	12	22	11	3.9
16	22	24	9	4.0
17	16	24	24	5.9
19	26	17	11	4.3
20	39	26	26	5.7
21	30	12	12	3.8
22	36	20	14	3.8
23	38	32	25	5.9
24	23	20	18	4.8
25	35	38	12	5.4
26	20	16	15	4.4
27	38	31	23	6.8
29	15	18	13	4.6
30	30	14	14	4.3
33	11	32	26	6.3
34	24	6	13	3.6

SUBJECTS' NUMBER	M.P.I. EXTRAV.	M.P.I. NEUROT.	TAYLOR ANXIETY	16PF ANXIETY
35	13	2	22	5.7
36	42	7	4	3.0
37	26	40	5	5.8
42	16	5	29	4.9
43	21	24	3	7.6
45	26	16	20	2.8
48	16	18	17	6.1
49	31	40	9	4.8
53	29	24	29	8.0
58	36	14	41	4.8
62	18	14	8	5.6
66	35	44	24	6.6
67	18	25	28	4.9
69	24	38	26	7.0
73	25	4	8	4.1
79	34	7	4	5.3
85	37	16	6	5.6
87	32	30	15	7.2
72	44	14	12	3.9
50	37	30	13	7.4
88	26	20	36	5.1
63	22	32	35	6.2
86	16	16	24	5.2
89	16	16	13	7.7

The Scores recorded by the Experimental Group of Subjects on the Four Suggestibility Tests.

SUBJECT'S NUMBER	BODY-SWAY TEST	ARM-BENDING TEST	INK BLOT TEST	Heat Illus-ION TEST.
1	5	1	0	0
2	-11	0	0	2
3	-3	1	0	0
4	10	0	0	2
5	0	1	0	2
6	-15	0	0	0
7	-20	0	1	0
8	0	6	0	1
9	0	0	0	1
10	32	1	0	1
11	3	0	0	1
12	0	0	0	0
13	20	5	0	1
14	7	0	0	2
15	43	3	0	0
16	96	5	0	0
17	0	3	0	2
18	4	1	0	0
19	3	0	0	0
20	17	3	0	0
21	3	1	0	1
22	1	1	0	0
23	-2	1	0	1
24	-4	0	0	0
25	20	0	1	2
26	-8	1	0	2
27	4	0	1	1
28	40	5	0	0
29	46	6	0	1
30	2	5	0	2
31	-1	0	0	0
32	13	0	0	2
33	-5	0	0	2
34	10	0	0	0
35	-5	1	0	2
36	5	1	0	0
37	5	1	0	0
38	15	2	0	0
39	-1	1	0	0
40	12	1	0	1
41	-10	1	0	0
42	2	0	0	0
43	7	0	0	2
44	0	0	0	2

The responses given by the 45 experimental subjects to items on the questionnaire, administered for four days under the pre-placebo condition.

SUBJECT'S NUMBER	DAY I	DAY II	DAY III	DAY IV
21	17	12	15	12
48	14	4	10	6
49	7	5	6	5
50	9	7	11	9
29	12	7	6	9
53	21	17	27	22
58	4	5	6	3
86	20	17	14	10
22	6	6	6	6
33	28	21	22	22
85	13	13	12	8
36	5	6	6	8
79	8	7	5	6
26	11	13	5	6
69	22	20	16	21
43	23	14	8	8
3	10	12	7	13
25	8	11	11	8
20	16	14	11	12
5	12	10	8	10

62	15	10	16	12
63	18	8	10	9
30	13	16	14	11
19	12	9	6	5
73	9	7	7	5
72	14	16	12	12
35	16	9	7	8
89	13	14	11	13
10	15	11	11	8
11	13	14	9	7
12	29	32	31	29
45	11	7	8	1
24	20	15	17	7
23	12	16	8	14
37	9	10	6	9
13	14	6	8	5
16	15	12	9	8
42	18	11	7	8
17	19	16	14	19
66	26	30	18	14
67	18	14	17	17
34	1	6	4	15
27	16	10	6	7
87	14	13	12	13
88	20	10	14	11

The responses given by 45 experimental subjects to items on the questionnaire, under the placebo condition.

SUBJECT'S NUMBER	DAY I	DAY II	DAY III	DAY IV
21	19	20	15	10
48	15 +1	8 +3	5	6
49	8	4	7	5
50	2	5	4	4
29	15	14	6 +1	10 +1
53	10	7	7	6
58	3	3	3	0
86	16	28	15	25
22	8 +1	14 +1	10	10
33	13 +3	11 +1	14	14
85	7 +1	7	7	6
36	6	5	0	5
79	6	5	3	2
26	9	5	3	2
69	15	10	10	16
43	3	9	9	3
3	7	5	6	4
25	14	13	20	7
20	6	8	5	1
5	11	15	13	13
62	11 +1	11	13	16

63	8	4	4	4
30	11	17	20	13
19	7	4	3	3
73	7	5	6 +4	5 +1
72	5	9	6	7
35	4	0	0	1
89	12	18	19	14
10	7	7	8	5
11	4	0	3	6
12	20 +2	22	23	14 +1
45	0	5	1	1
24	5	15 +1	11 +1	2
23	11	12 +4	11 +3	15
37	6	6	5	4
13	4 +2	11	12 +3	9
16	14	4	3	5
42	3	3	7	3
17	8 +1	8	3	5 +1
66	8 +1	11	13	4
67	9 +1	10	12	9
34	4 +3	7 +1	0	3
27	8	8	5	5
87	10	5	10 +2	12 +1

88	12 +1	12	12	12

* All additional figures are numbers of symptoms reported by subjects after taking placebo which were not listed as possible items. They were not used in the statistical comparison.

The Response Frequency for Each Item of the Questionnaire Reported by 45 Experimental Subjects While Taking Placebo.

SYMPTOM NUMBER	TOTAL F DAY I	%	TOTAL F DAY II	%	TOTAL F DAY III	%	TOTAL F DAY IV	%	$\bar{X}$ %
1	17	38	14	31	14	31	12	27	31.7
2	3	6	3	6	2	4	4	9	6.2
3	1	2	7	15	5	11	5	11	9.7
4	1	2	3	6	2	4	3	6	4.7
5	3	6	0	0	0	0	0	0	1.5
6	7	15	4	9	7	15	4	9	12.0
7	2	4	2	4	1	2	1	2	3.0
8	4	9	2	4	2	4	0	0	4.2
9	10	22	6	13	7	15	8	18	17.0
10	4	9	5	11	6	13	6	13	11.7
11	4	9	3	6	5	11	3	6	8.0
12	0	0	1	2	1	2	3	6	2.7
13	3	6	1	2	2	4	2	4	4.0
14	6	13	5	11	4	9	2	4	9.2
15	2	4	1	2	3	6	4	9	5.2
16	3	6	6	13	5	11	2	4	8.7
17	3	6	8	18	2	4	3	6	8.7
18	4	9	7	15	5	11	7	15	12.7
19	4	9	5	11	4	9	5	11	10.0
20	10	22	5	11	6	13	6	13	14.7
21	31	70	30	68	21	47	11	38	55.7
22	9	20	11	25	11	25	6	13	20.7

SYMPTOM NUMBER	TOTAL F DAY I	%	TOTAL F DAY II	%	TOTAL F DAY III	%	TOTAL F DAY IV	%	$\overline{X}$ %
23	3	6	4	9	2	4	1	2	5.2
24	8	18	7	15	9	20	5	11	16.0
25	29	65	23	52	17	38	14	31	46.5
26	21	49	21	47	16	36	14	31	40.7
27	12	27	8	18	7	15	9	20	20.0
28	4	9	4	9	1	2	3	6	6.5
29	8	18	12	27	12	27	8	18	22.5
30	5	11	9	20	10	22	6	13	16.5
31	1	2	3	6	1	2	0	0	2.5
32	1	2	3	6	2	4	1	2	3.5
33	1	2	3	6	1	2	2	4	3.5
34	2	4	4	9	4	9	6	13	8.7
35	2	4	3	6	2	4	3	6	5.0
36	2	4	3	6	5	11	2	4	6.2
37	6	13	9	20	6	13	3	6	13.0
38	2	4	0	0	2	4	10	22	7.5
39	4	9	13	29	12	27	2	4	17.5
40	0	0	3	6	3	6	5	11	5.7
41	6	13	5	11	8	18	0	0	10.5
42	1	2	4	9	1	2	0	0	3.2
43	2	4	4	9	1	2	1	2	4.2
44	4	9	17	38	3	6	1	2	13.7
45	23	52	9	20	16	36	15	34	40.5
46	13	29	15	34	13	29	12	27	29.7

SYMPTOM NUMBER	TOTAL F DAY I	%	TOTAL F DAY II	%	TOTAL F DAY III	%	TOTAL F DAY IV	%	$\bar{X}$ %
47	23	52	15	34	20	45	16	36	41.7
48	16	36	16	36	14	31	19	43	36.5
49	15	34	12	27	16	36	15	34	32.5
50	7	15	15	34	11	25	11	25	24.7
51	8	18	9	20	10	22	7	15	18.7
52	16	36	12	27	7	15	8	18	24.0
53	13	29	9	20	11	25	11	25	24.7

The Response Frequency for Each Item of the Questionnaire Reported by 45 Experimental Subjects While in the Pre-Placebo Condition.

SYMPTOM NUMBER	TOTAL F DAY I	%	TOTAL F DAY II	%	TOTAL F DAY III	%	TOTAL F DAY IV	%	$\bar{X}$ %
1	17	38	4	9	13	29	11	25	25.2
2	0	0	3	6	2	4	3	6	4
3	7	15	7	15	1	2	3	6	9.5
4	3	6	4	9	4	9	2	4	7.0
5	6	13	5	11	3	6	1	2	8.0
6	11	25	6	13	2	4	0	0	9.5
7	3	6	1	2	3	6	2	4	4.5
8	0	0	1	2	2	4	1	2	2.0
9	12	27	8	18	4	9	4	9	15.7
10	2	4	4	9	4	9	2	4	6.5
11	6	13	5	11	6	13	3	6	10.7
12	1	2	1	2	2	4	0	0	2.0
13	5	11	3	6	4	9	5	11	9.2
14	2	4	2	4	1	2	1	2	3.0
15	11	25	8	18	10	22	10	22	21.7
16	9	20	7	15	5	11	7	15	15.2
17	13	29	8	18	10	22	9	20	22.5
18	16	36	6	13	6	13	7	15	16.7
19	8	18	5	11	4	9	5	11	10.7
20	16	38	13	29	10	22	9	20	26.7
21	31	70	32	71	24	53	24	53	61.7
22	6	13	5	11	7	15	8	18	14.3

SYMPTOM NUMBER	TOTAL F DAY I	%	TOTAL F DAY II	%	TOTAL F DAY III	%	TOTAL F DAY IV	%	$\bar{X}$ %
23	2	4	2	4	3	6	2	4	4.5
24	3	6	6	13	7	15	7	15	12.2
25	30	67	31	70	30	67	29	65	67.2
26	15	34	15	34	8	18	8	18	26.0
27	24	53	21	47	16	38	16	38	44.0
28	5	11	3	6	6	13	4	9	9.7
29	19	43	19	43	16	38	11	25	37.2
30	9	20	6	13	9	20	9	20	18.2
31	5	11	1	2	1	2	0	0	3.7
32	5	11	6	13	5	11	3	6	10.2
33	9	20	9	20	5	11	3	6	14.2
34	11	25	9	20	7	15	11	25	21.2
35	8	18	5	11	7	15	4	9	13.2
36	11	25	6	13	9	20	6	13	17.7
37	13	29	11	25	13	29	10	22	26.2
38	11	25	7	15	5	11	2	4	13.7
39	22	48	19	42	18	40	13	29	39.7
40	8	18	6	13	4	9	4	9	12.2
41	24	53	11	25	11	25	7	15	29.5
42	3	6	2	4	2	4	3	6	5.0
43	3	6	4	9	2	4	1	2	5.2
44	10	22	7	15	7	15	4	9	15.2
45	19	43	13	29	13	29	15	34	33.7
46	15	34	12	27	9	20	9	20	25.2

SYMPTOM NUMBER	TOTAL F DAY I	%	TOTAL F DAY II	%	TOTAL F DAY III	%	TOTAL F DAY IV	%	$\bar{X}$ %
47	29	65	32	71	30	67	29	65	67.2
48	38	84	36	80	34	75	33	73	78.0
49	36	80	36	80	34	75	33	73	77.0
50	25	55	24	53	18	40	21	47	48.7
51	14	31	10	22	10	22	8	18	23.2
52	18	40	19	42	19	42	27	60	46.0
53	23	52	12	27	11	25	7	15	29.7

FIGURE 1: The percentage of 45 experimental subjects responding positively to the items of the Questionnaire on Day 1 of the pre-placebo condition.

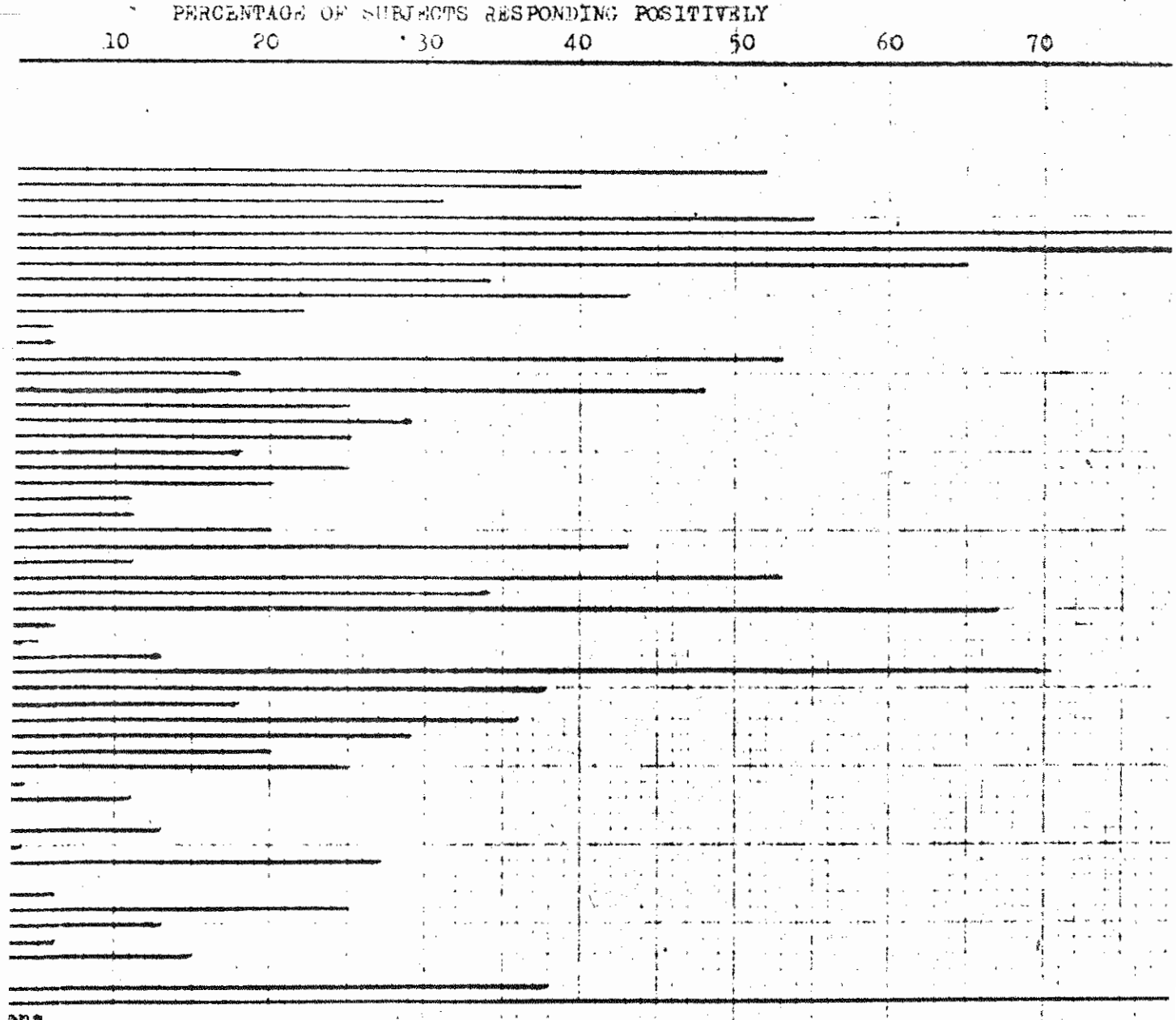


FIGURE 2: The percentage of 45 experimental subjects responding positively to the items of the Questionnaire on Day of the pre-placebo condition.

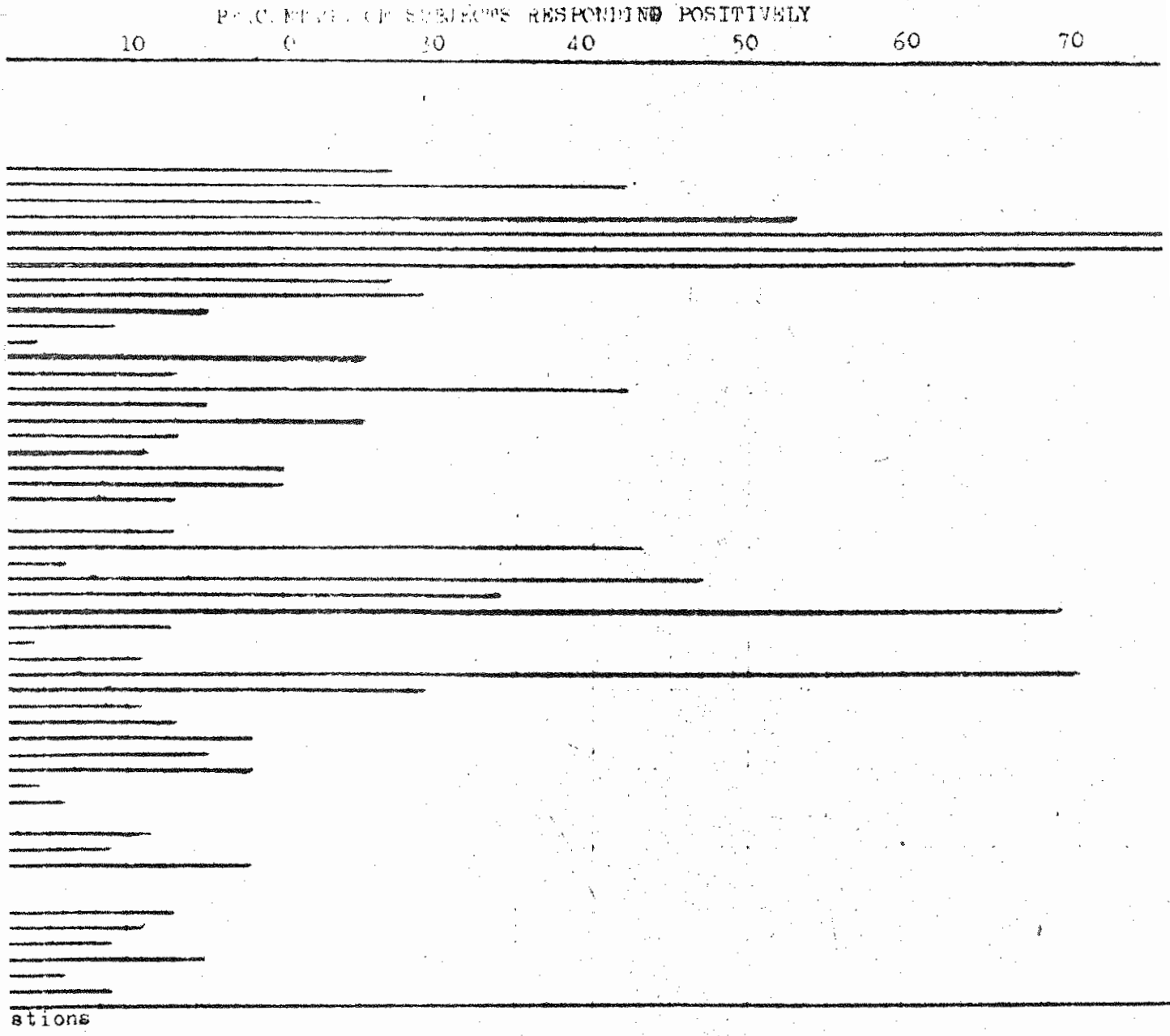


FIGURE 3: The percentage of 45 experimental subjects responding positively to the items of the Questionnaire on Day 3 of the pre-placebo condition.

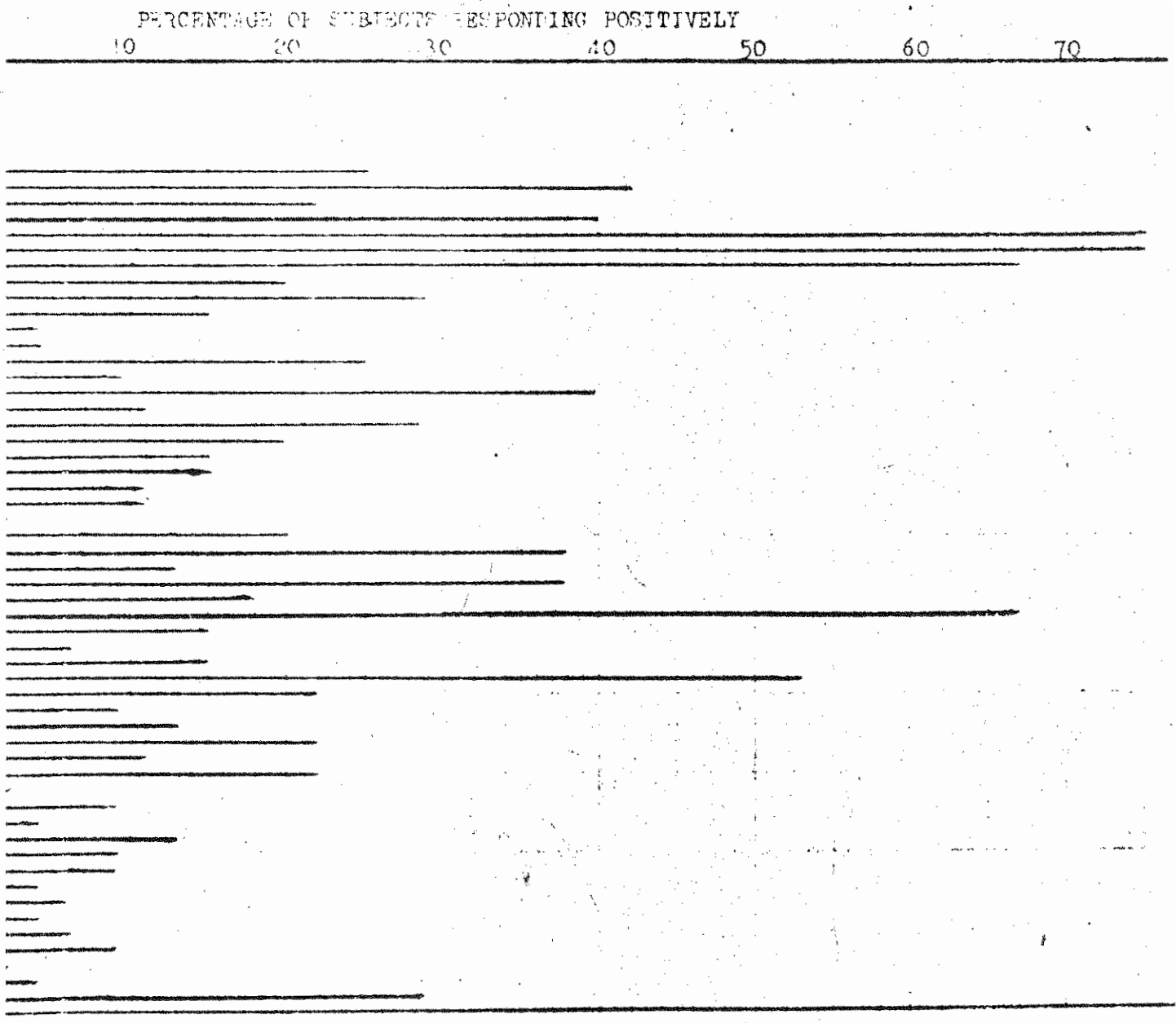


FIGURE 4: The percentage of 45 experimental subjects respondi positively to the items of the Questionnaire on Day 4 of the pre-placebo condition.

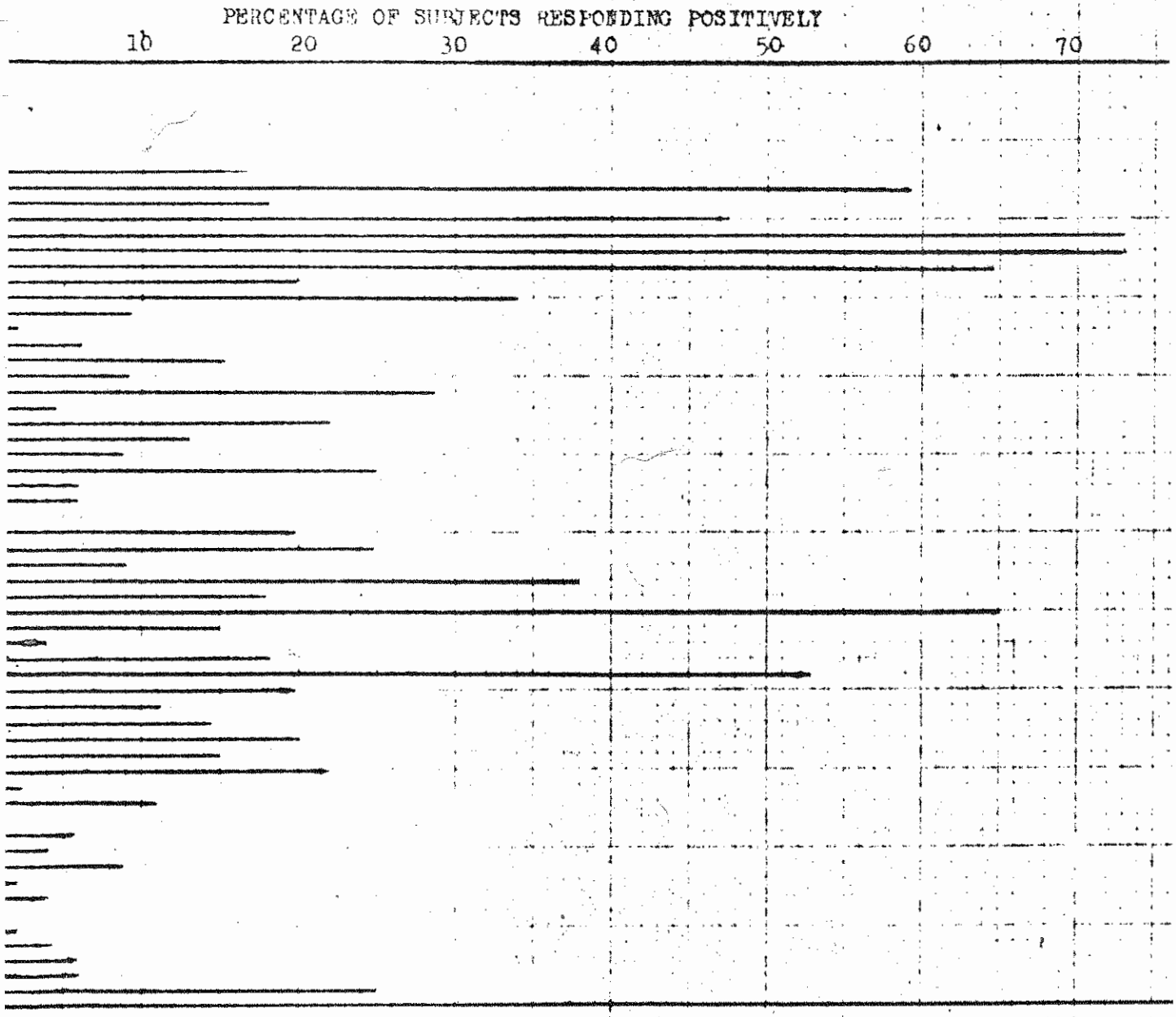


FIGURE 5 : The Percentage of 45 Subjects Responding Positively to the Items of the Questionnaire on Day I while receiving placebo.

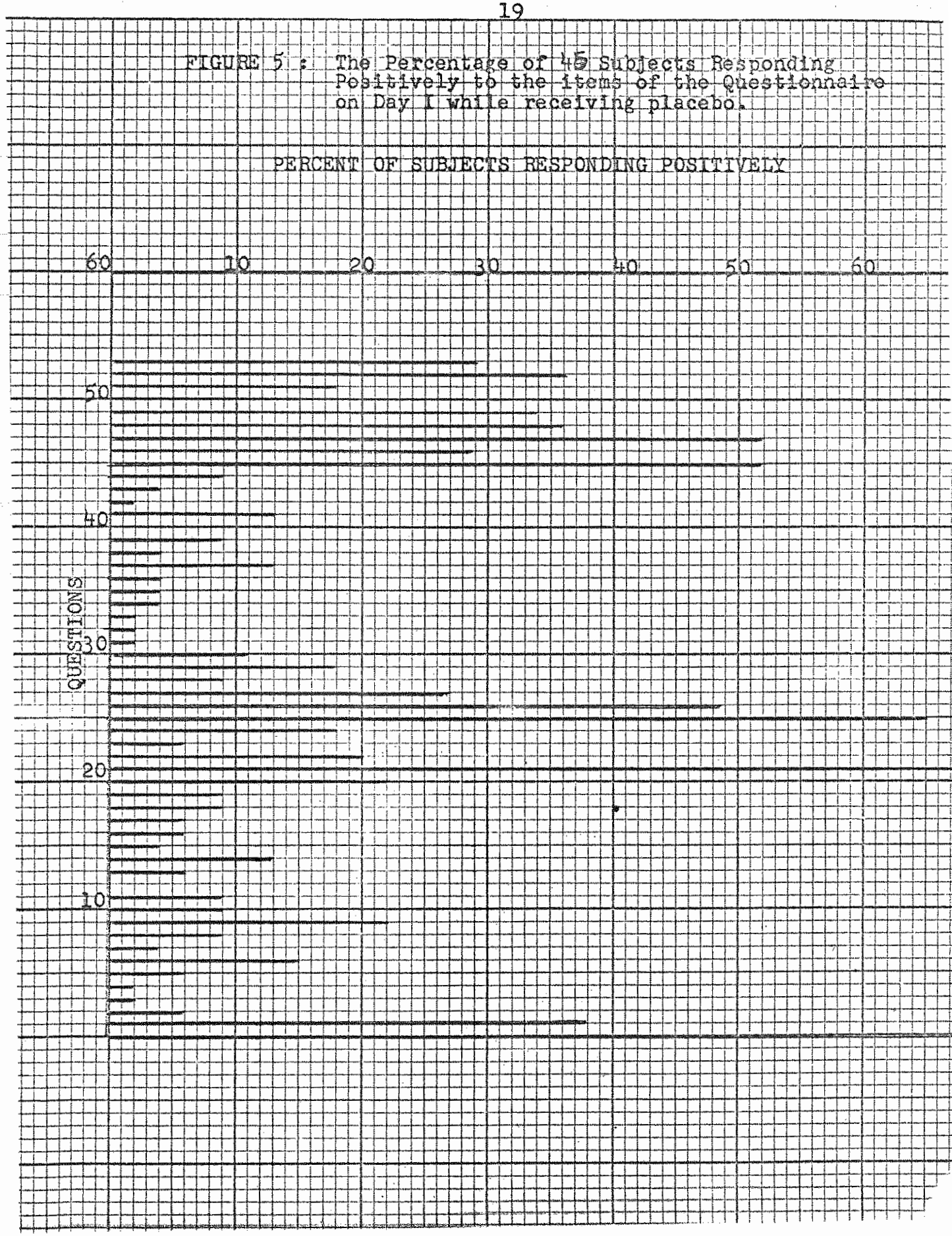


FIGURE 6 : The Percentage of 45 Subjects responding Positively to the items of the Questionnaire on Day II while receiving placebo.

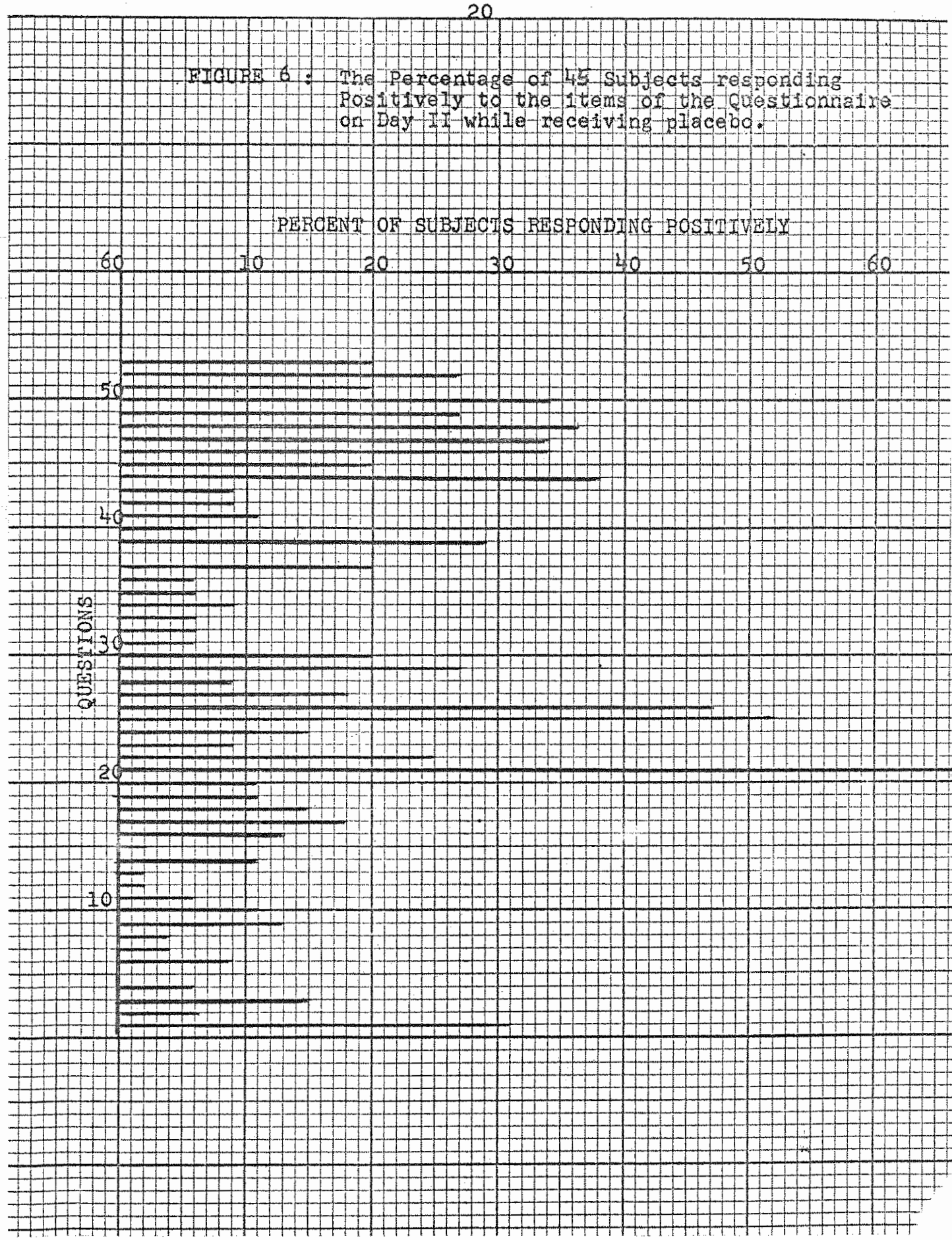


FIGURE 7: The Percentage of 45 Subjects Responding Positively to the items of the Questionnaire on Day III while receiving placebo.

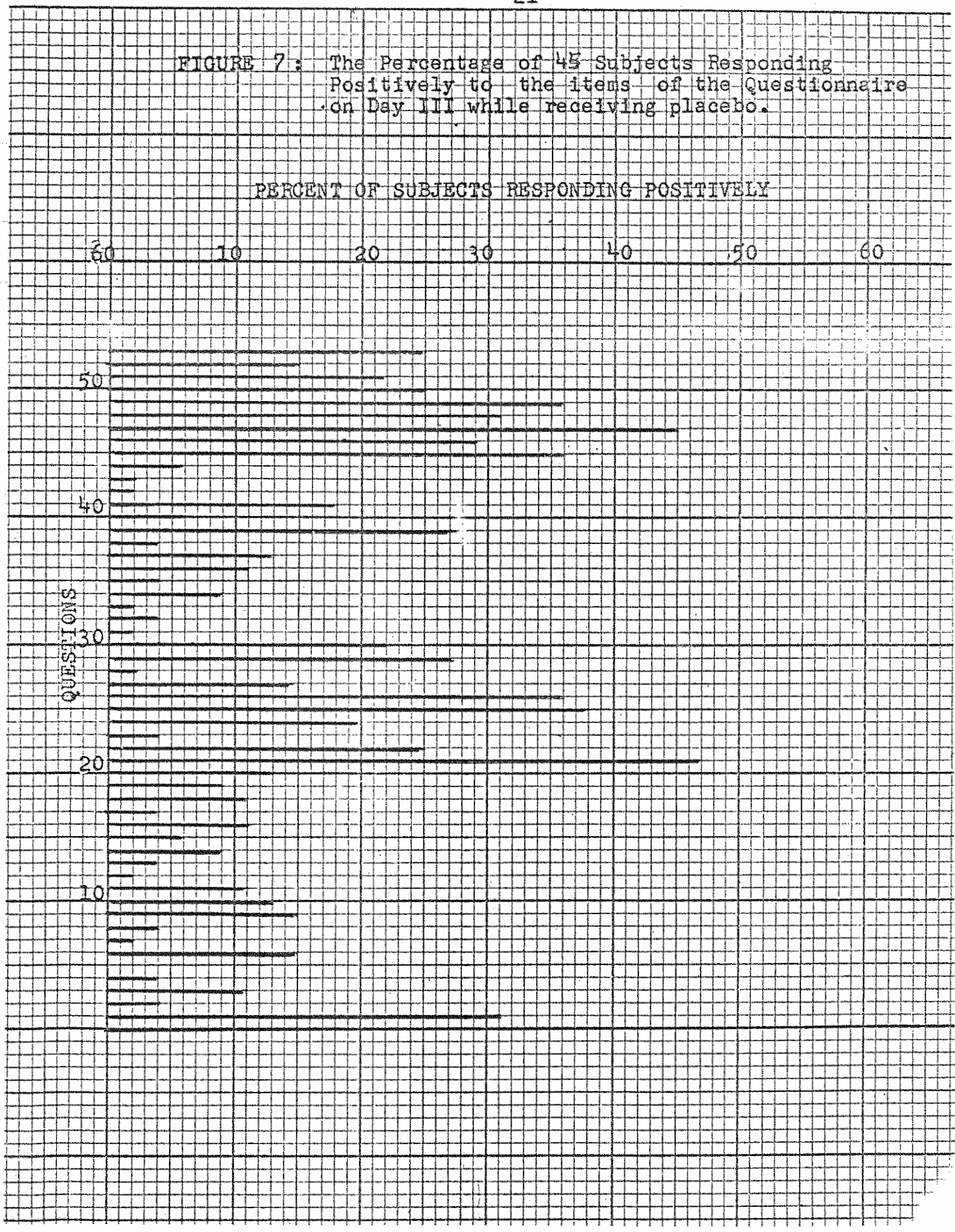
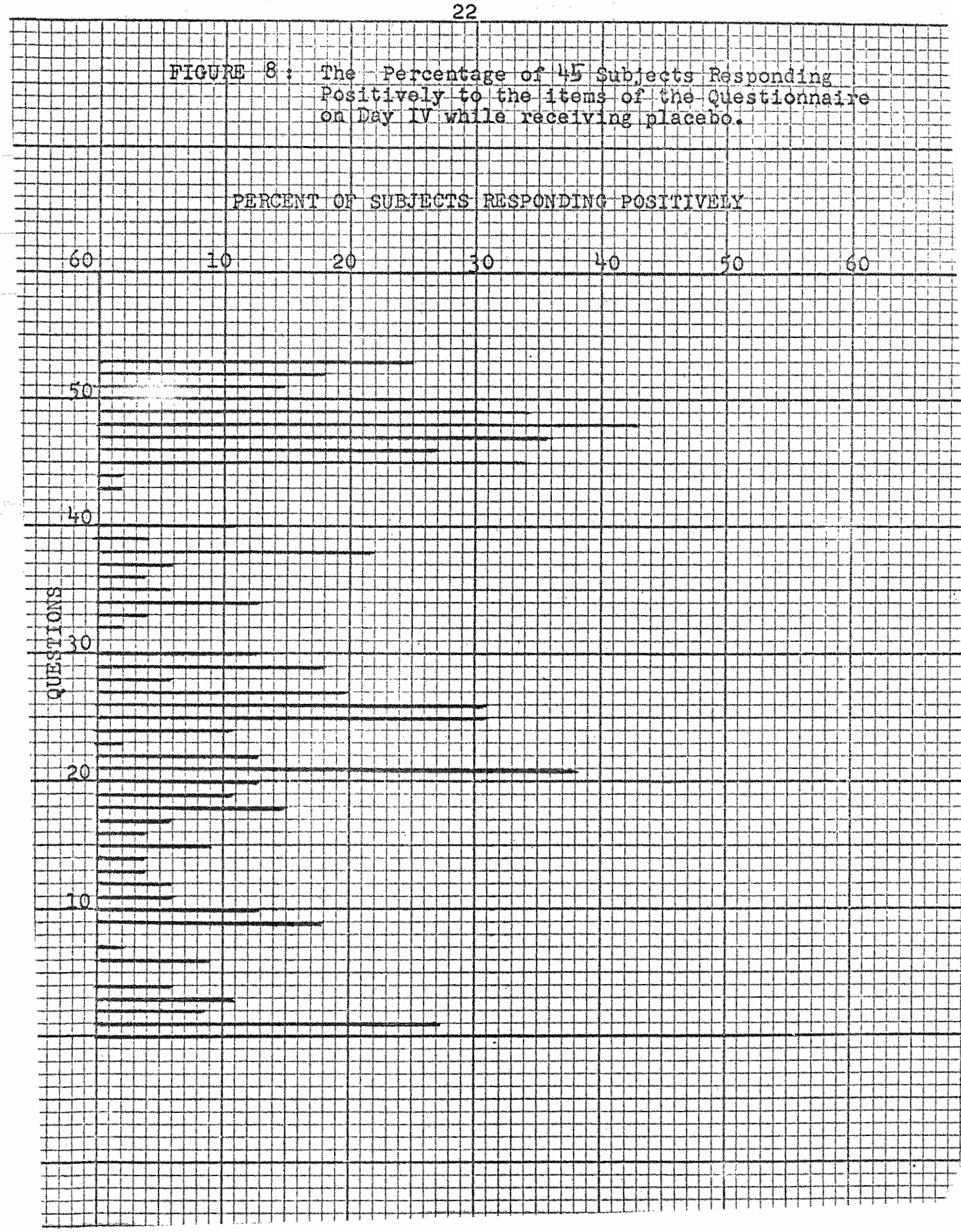


FIGURE 8: The Percentage of 45 Subjects Responding Positively to the Items of the Questionnaire on Day IV while receiving placebo.



The total number of toxic symptoms reported by 45 experimental subjects for 4 days, under the pre-placebo condition.

SUBJECT'S NUMBER	DAY I	DAY II	DAY III	DAY IV
21	13	11	10	8
48	9	3	5	3
49	3	1	1	2
50	6	6	8	6
29	8	2	2	3
53	20	15	21	18
58	0	2	3	0
86	13	11	9	9
22	0	0	0	0
33	21	14	17	15
85	11	10	9	6
36	2	1	1	2
79	3	3	0	1
26	7	7	6	0
69	14	12	11	14
43	17	12	7	7
3	5	12	2	7
25	2	6	7	2
20	10	9	10	7
5	7	4	3	3
62	13	8	11	8
63	18	9	7	4

SUBJECT'S NUMBER	DAY I	DAY II	DAY III	DAY IV
30	7	11	9	6
19	8	3	1	0
73	5	2	1	0
72	7	9	5	7
35	13	9	2	2
89	8	8	5	9
10	11	6	6	6
11	9	11	5	3
12	30	30	25	27
45	8	5	6	1
24	13	8	14	4
23	7	9	2	6
37	3	4	0	2
13	7	1	4	2
16	9	9	4	4
42	13	8	4	3
17	12	12	10	15
66	24	26	14	9
67	11	13	14	11
34	0	2	0	11
27	12	5	0	2
87	9	8	8	10

The total number of Toxic Symptoms reported by the 45 experimental subjects for 4 days under the placebo condition.

SUBJECT'S NUMBER	DAY I	DAY II	DAY III	DAY IV
21	11	13	12	7
48	11	7	4	6
49	5	2	3	2
50	2	4	3	2
29	9	12	2	5
53	10	7	7	6
58	3	3	2	0
86	10	25	9	22
22	3	10	6	7
33	10	6	8	11
85	5	6	7	4
36	0	1	0	1
79	2	1	1	2
26	6	2	3	2
69	12	3	7	9
43	3	7	7	1
3	4	2	3	1
25	14	12	17	7
20	2	4		5
5	11	14	12	11
62	8	8	7	1
63	2	4	1	0

SUBJECT'S NUMBER	DAY I	DAY II	DAY III	DAY IV
30	8	12	15	12
19	4	2	0	0
73	6	5	6	5
72	3	5	3	3
35	4	0	0	1
89	7	15	16	11
10	5	5	7	4
11	1	0	3	6
12	12	16	17	6
45	0	2	1	1
24	5	14	11	2
23	10	12	8	14
37	0	0	0	0
13	1	6	10	4
16	10	4	1	0
42	3	2	6	3
17	7	6	3	5
66	3	6	8	0
67	7	6	7	3
34	2	4	0	0
27	2	6	2	2
87	9	3	9	10
88				

The placebo reaction scores of the Experimental Subjects (i.e. the total number of changes in response reported by the subjects for Day 4 to Day 5 and Day 3 to Day 6).

SUBJECT'S NUMBER	CHANGES, DAY 4 TO 5	CHANGES DAY 3 TO 6
1.	10	13
2.	14	14
3.	4	3
4.	2	6
5.	6	16
6.	15	23
7.	5	27
8.	25	3
9.	10	11
10.	12	21
11.	11	11
12.	2	1
13.	3	4
14.	9	4
15.	13	11
16.	9	9
17.	13	6
18.	11	12
19.	14	14
20.	18	16
21.	19	16
22.	5	12
23.	13	21
24.	5	4
25.	13	12
26.	8	9
27.	6	12
28.	12	7
29.	10	17
30.	11	9

SUBJECT'S NUMBER	CHANGES, DAY 4 TO 5	CHANGES DAY 3 TO 6
31.	29	26
32.	1	11
33.	8	13
34.	21	16
35.	3	0
36.	3	11
37.	11	12
38.	9	6
39.	24	16
40.	12	15
41.	10	19
42.	11	15
43.	3	8
44.	12	5

Correlations between the placebo reaction scores of the experimental group of subjects and their personality test scores.

	1	2	3	4	5	6	7	8	9	10	11
1.	-										
2.	42	-									
3.	35	60	-								
4.	25	41	72	-							
5.	-01	-11	04	21	-						
6.	14	-22	-07	00	57	-					
7.	-11	22	20	-01	-09	19	-				
8.	-22	-27	-33	-21	-13	-06	05	-			
9.	-30	-19	-24	-12	-22	-15	06	05	-		
10.	87	50	39	32	-04	04	-19	-27	-33		
11.	02	13	06	32	-09	18	-04	12	29	10	-

LEGEND:

1. Placebo reaction score (Diff. Day 4 & 5).
2. Placebo reaction score (Diff. Day 3 & 6).
3. T.M.A.S. scores.
4. M.P.I. Neuroticism scores.
5. Body Sway scores
6. Arm Bending scores.
7. Ink Blot Test scores.
8. Heat Illusion Test scores.
9. M.P.I. Extraversion scores.
10. Degree of Placebo reaction Day 4 & 5.
11. Degree of Placebo reaction Day 3 & 6.