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Double-blind study of a new analgesic combination

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A DOUBLE-BLIND STUDY OF A NEW ANALGESIC COMBINATION

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HISTORY

The search for the relief of pain has occupied the minds of men since before the periods of recorded time. The history of anesthesia-analgesia reveals that possibly the first reference to anesthesia occurred about 4000 B.C.: "And the Lord God caused a deep sleep to fall upon Adam, and he slept; and He took one of his ribs, and closed up the flesh instead thereof." Genesis II:21 (41). Man turned early to his natural surroundings, knowing little of the mechanism or nature of pain, but seeking to relieve suffering with the materials provided by nature. A clay tablet dated to Babylon about 2250 B.C. proposed a remedy for the relief of toothache. Theophrastus wrote of hellebore for the relief of pain in the 4th century B.C., (12) Circa 540 B.C., Sirsuta in India mentioned the use of henbane and hemp to produce insensibility and the effects of pressure on nerves and blood vessels was known by the early Egyptian surgeons (41). Little progress was made during the Dark Ages. "Sweet vitriol" was discovered about 1275 by Raymundus Lullius in Spain; and again 200 years later by Paracelsus, who recognized its effects (41). Valerius Cordis, in 1543, described its synthesis as ether. But its use as an anesthetic was delayed for many centuries (41). As early as 1513, monks used the dulling effect of alcohol. Pare, in 1564, used pressure to induce anesthesia, thousands of years after its discovery by the Greeks and Egyptians (41). The independent discovery of oxygen by Priestly and Scheele led to the understanding of its significance by Lavoisier in 1792 (12). These

discoveries were the forerunners of the administration of medicines by inhalation. These findings also became the basis for work by Sir Humphrey Davy with nitrous oxide, by Michael Faraday with ether, and by Henry Hill Hickman with carbon dioxide (7). Although these men published extensively, their contributions were not to be recognized in their day, nor for many years to follow. Franz Anton Mesmer, 1776, reported experiments with "animal magnetism"; and this process was used by Jules Cloquet, a French surgeon, to successfully perform a mastectomy on a mesmerized patient (12). Although the search for pain relieving agents had proceeded over thousands of years, it remained for four men, within the short span of four years to accomplish a massive breakthrough. Crawford W. Long, the first to use ether in surgery, in Georgia, and the dentist Horace Wells, in Connecticut, appreciated the effects of ether and nitrous oxide at a backwoods "ether frolic" and a "laughing gas" demonstration by an itinerant chemist, respectively (51). In spite of Well's tragic failure with nitrous oxide before surgeons at Massachusett's General Hospital, W. T. G. Morton stimulated the start of systematic study and experimentation; and later successfully demonstrated the use of ether anesthesia (17). It was Morton's persistence in working out a technique for the administration of ether that made satisfactory anesthesia possible. Because Morton could not achieve consistent results, he consulted Dr. Charles T. Jackson who suggested the use of highly purified ether which thus led to better and more consistent results. On the morning of October 16, 1846, Gilbert Abbott

was prepared for operation at the Massachusetts General Hospital in Boston. Dr. Warren, a highly reputable surgeon and one of Morton's instructors, had agreed to a demonstration of Morton's apparatus. Present were many other prominent surgeons; among them were Heywood, Bieglow, Gould and Townsend (12). Postoperatively, Abbott said that he had felt no pain, only a scratching sensation. Dr. Warren is reported to have turned to the audience and said: "Gentlemen, this is no humbug" (12). Thus the beginnings of anesthesia. Claims and counterclaims regarding rights to priority and patents ensued, removing some of the luster from the sheen of the discoverers. Although patents had been issued to Morton, even Government agencies ignored them and proceeded with the use of ether.

The controversy as to the just recipient of credit for the discovery of ether still persists. Long was undoubtedly the first to use ether in an operation. But as Robinson pointed out; "Long's first use of ether was of importance to no one except the four or five patients upon whom he used it, and for four years, ether remained unknown and unavailable to the world whose pain it might have relieved" (12). Of Wells, Keyes wrote; "...although Wells failed to convince the world of the value of nitrous oxide, he is credited with conceiving the idea of anesthesia and publicizing the possibility of its use" (12). Of the four, Jackson has had the fewest supporters. Cartwright (18) said; "...of one thing there is no doubt, the general acceptance of anesthesia dates from Morton's successful demonstration of anesthesia October 16, 1846. Within a year, hardly an operation was performed

throughout the civilized world without the use of ether." To these men and to many others a debt of gratitude is owed. Dr. Oliver Wendell Holmes summed it: "... by this priceless gift to humanity, the fierce extremity of suffering has been steeped in the waters of forgetfulness, and the deepest furrow in the knotted brow of agony has been smoothed forever" (12).

Upon the heels of these monumental discoveries, shortly followed the discovery of chloroform, spinal anesthetics, synthetics and all the refinements of modern anesthesia.

Much effort has also been applied to the search for the ideal analgesic agent. That is has not been found, is apparent from the continuing search.

The history of opium also dates to the earliest days of recorded history. Opium is mentioned in Assyrian medical tablets and the Ebers papyrus, supposedly written about 1552 B.C. (45). In the 2nd century, Galen wrote enthusiastically of its virtues. Modern tincture of opium or laudanum was introduced by Paracelsus. In 1803, an apothecary's assistant, a young German named Serterner, isolated an active constituent of opium as crystalline morphine. Thus was issued in a new era in the field of analgesia (61). Because of recognition of several of the serious defects of morphine, i. e. respiratory depression, nausea, emesis and addiction, the search for the ideal analgesic continued. Each of the synthetic narcotic agents subsequently developed for clinical use has been shown to be addicting and to have a pharmacological spectrum similar to that of morphine. Certain of these agents

have been found to be of advantage in particular situations and have been used extensively; of these, mederidine has enjoyed considerable popularity. Concurrently with the development of the narcotic analgesics, naturally occuring non-narcotic forms of the salicylates had been known for thousands of years. They were known to Hippocrates and were used by Galen. Their use as an antipyretic was first mentioned in 1763. In 1876, salicylates were first used in rheumatic fever and about 20 years later aspirin was introduced into medical practice. Extensive reviews of the salicylates have been prepared by Gross and Greenberg (34) and Smith (56). Aspirin is probably the most widely used, and in the largest quantity, therapeutic agent in the world today. Today, morphine and aspirin still stand high, if not supreme, in the hierarchy of analgesia.

Alstead (3), in his work on the philosphical background of pain and analgesia, pointed out that man has shown reluctance to regard pain as a phenomenon calling for analysis and understanding; but has regarded it as intrinsically evil. A large proportion of the ingenuity of pharmaceutical companies has been devoted to the search for the perfect analgesic, a concept almost as illusory as the perfect man. Pain is a subjective sensation, and as such extremely difficult to measure quantitatively. The individual's pain threshold depends upon his emotional make-up and previous conditioning and may vary from day to day depending on mood and other psychological factors (36). Another major problem in the study of pain and its relief is that of evalu-

ation of the analgesic effect. Methods developed have depended upon graded thermal, mechanical or electrical effects, or the relief of surgical pain. None has proved entirely satisfactory.

It is well to remember that the psychological consequences of pain and analgesia may be far-reaching and complex.

THE DRUG

The drug* studied is a three layered, yellow, white and pink tablet consisting of:

White layer: Meprobamate - 150 mg.

Yellow layer: Ethoheptazine citrate - 75 mg.

Pink layer: Acetylsalicylic acid - 250 mg.

Meprobamate was found in a search for a longer-acting, orally effective substance with actions similar to mephenesin. Chemically, meprobamate is a propanediol derivative and therefore has some chemical relationship to mephenesin. (see Figure 1)

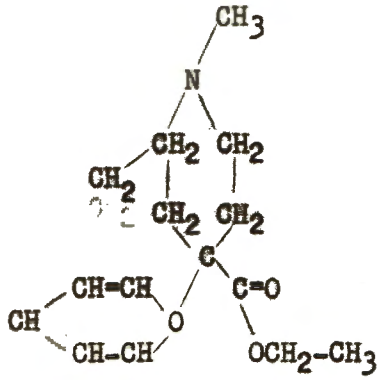
MEPROBAMATE MEPHENESIN

FIGURE 1

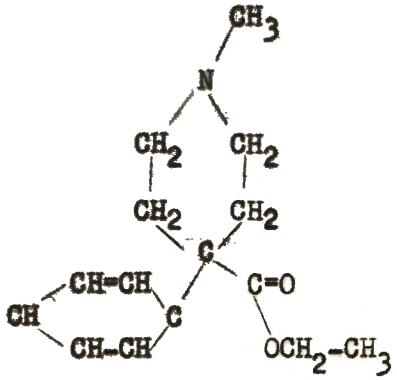
It shares with mephenesin an effect on the spinal cord, polysynaptic reflexes particularly being depressed. In contrast with mephenesin, meprobamate has been reported to have more profound anticonvulsant properties and a muscle-relaxant effect of longer duration. The drug has also shown that anticonvulsant effect in experimental animals. It has also been stated that meprobamate exerts a subtle, relaxing effect on disturbed patients. It has no appreciable effect on organs and tissues outside the central nervous system (60). The pharmacological actions and properties of meprobamate have been carefully studied and described by Berger (13, 14, 15) and Walkenstein (67).

*EQUAGESIC

Ethoheptazine citrate is a racemic mixture of the d and l isomers of 1-methyl-4-carbethoxy-4-phenyl hexamethylenimine. It is related to meperidine, differing in that it contains a seven-membered heterocylic ring in place of the pipericline ring. (see Figure 2) Previous studies have demonstrated the general pharmacological properties and analgesic potency in animals (20, 29, 30, 66). Clinical effectiveness and safety of this compound have been reported by Glassman (31), Grossman (35) and Golbey (32). In summary, these authors found that ethoheptazine is an active analgesic not causing sedation, constipation, neurological manifestations such as suppression of the cough reflex or changes in pupil size, nor does it cause disorientation. In addition, there has been no evidence that ethoheptazine has any addiction liability (25, 47).



ETHOHEPTAZINE



MEPERIDINE

FIGURE 1

Serious side effects have not been observed. A small number of patients may experience nausea, vomiting or epigastric distress. Dizziness occurs rarely. Meprobamate may cause drowziness, but this generally disappears with continuation of therapy. If drowziness persists, de-

creasing the dose usually controls the symptom. In a small number of patients, meprobamate has caused severe allergic reactions and thus should not be administered to individuals with a history of hypersensitivity or patients with past reactions to meprobamate or aspirin. Mild allergic reactions are characterized by a pruritic, urticarial, erythematous rash, generalized or localized. Treatment is that of hypersensitivity reactions; the administration of epinephrine, antihistamine and possibly steroids in very severe cases.

The pharmacology, chemistry and toxicology of acetylsalicylic acid may be found in any good pharmacology textbook. It would be well to mention one lone point. It has been shown that the analgesic actions of acetylsalicylic acid are due to the depression of pain impulses through the hypothalmus without impairment of cortical function, and thus, no hypnotic effect (63).

The first clinical study on meprobamate by Selling (55) reported that meprobamate was a practical, safe and clinically useful central nervous system depressant; of most value in the anxiety neurosis syndrome. Equally good results were reported in the tense, nervous and emotionally distressed patient by other authors (59, 70). Dixon (23) had very gratifying results in tension headaches, with an 86% relief rate as contrasted with a 23% relief rate in migraine or cephalagia. Good results with chronic headache were also reported by Blumenthal (16) who demonstrated that chronic headache almost always included tension or anxiety in its etiology; and that even in vascular headache such as migraine, tension was important in its causation and could

prolong its severity. Friedman (27) confirmed these results. Some of the best results with meprobamate have been reported in connection with its use as a muscle relaxant compound, especially in those conditions in which there is an associated emotional tension or anxiety (20, 21, 28, 37, 64). Other studies have shown meprobamate to be of value in rheumatic diseases (57), in premenstrual stress (55), in dysmenorrhea (48), in the treatment of alcoholics (65), and in the therapy of allergic disorders (64). Mitchell (48) found that the addition of acetylsalicylic acid enhanced the effect of meprobamate alone.

Batterman et. al. (6) have shown that ethoheptazine differed from other potent analgesics of the meperidine type in that it did not: 1. provoke morphine like excitement; 2. cause lethargy; 3. depress respiratory function before circulatory failure; and 4. antagonize the action of barbiturates in experimental animals. Also, in a large series conducted with ambulatory and hospitalized patients suffering from a wide variety of complaints, he found ethoheptazine to be an effective analgesic. 73% of ambulatory patients with musculoskeletal pain as their chief complaint were relieved satisfactorily. Of these, 4% had anorexia, nausea or dizziness. In the hospitalized group, in doses of 50 mg q day, 48.2% received satisfactory relief with no side reactions. In doses of 100 mg q day, 61.8% received satisfactory relief, with again a 4% side reaction rate. Best relief was obtained with musculoskeletal pain and the drug was not effective in very severe pain or most headaches. He also found that combination with acetyl-

salicylic acid enhanced ethoheptazines analgesic effect. Other authors have reported on the combination of ethoheptazine and aspirin producing satisfactory analgesia (2, 38). Cass (19) reported that ethoheptazine and aspirin were potent analgesics when given singly, and that when given together their combined effect was greater than that of either given alone. Ethoheptazine, 100 mg, was shown to be more efficient than 600 mg of aspirin. 600 mg of aspirin plus 100 mg ethoheptazine was shown to be equivalent to 30 mg of codeine and 600 mg of aspirin; but attendant side effect were significantly reduced. Barber (4) and Irby (40) also reproduced these findings. Many authors have reported on satisfactory relief of post-partum pain in more than 90$ of patients in their series with this combination of ethoheptazine and aspirin (6, 46, 52). Side effects in all cases were reported as minimal and confined primarily to drowziness. In no case, did undesirable side effects necessitate discontinuation of treatment. Authors were in general agreement that the combination of ethoheptazine and acetylsalicylic acid satisfied the requirements of a moderately potent analgesic for moderate to severe pain with a minimum number of side effects.

Splitter (58) in one of the few early reports on the combination of meprobamate, ethoheptazine citrate and aspirin, stated that it was "highly effective" in a private practice group of patients suffering with muscle spasm, anxiety, tension or apprehension.

METHOD

The purpose of this study was to attempt to determine the relative analgesic effectiveness of the combination of meprobamate, ethoheptazine citrate and acetylsalicylic acid. It has been demonstrated that appraisal of drugs for clinical relief of pain should adhere to conditions under which these drugs will be actually used (35). For this reason, the study was conducted with both an ambulatory and a hospitalized group of patients. No attempt was made to select patients on the basis of diagnosis, severity or duration of pain. The double-blind technique was used. Briefly, this is a device used to prevent bias from affecting the results. It rules out the possible prejudices or anxieties of the patient by giving both the drug under investigation and a placebo of identical appearance in such a way that the subject does not know which he is receiving. It also rules out the bias or influence of the investigator by keeping him ignorant of whether he is prescribing active drug or placebo. At the same time, the method provides comparison between the magnitude of effect between drug and placebo. The method can further be expanded to include a third drug which may also be used for relative comparisons.

The device is both philosophically and practically sound. Yet, an inherent error has arisen in the use of the method in assuming that it is a complete method for drug evaluation. It must be remembered that in a large number of studies in which the technique has been employed, the conclusions are open to question (42). Used properly, the

validity of the double-blind technique for the evaluation of drugs in comparable situations has been confirmed extensively (26, 39, 42, 49). For a complete and comprehensive description of the double-blind technique, see Wang (68).

In this study three different medications were used; the first being the experimental combination under study, the second being 250 mg of acetylsalicylic acid, and the third an inert placebo. All three medications were identical in appearance, shape and taste. The tablets were contained in 600 similar bottles of 20 tablets each. Each bottle was labeled MDS 83. The bottles were further coded by number from 1 to 600. One-third of the bottles were filled with each of the medications, the bottles having been selected at random. A decoding list was then prepared* and placed in a sealed envelope. Findings were tabulated by the use of the code number. Results were not decoded and transposed until the study was completed.

The hospitalized group consisted of post-partum patients on a University Obstetrical Service. The medication was prescribed by attending staff as 'Routine analgesic, MDS 83' for all post-partum patients. Dosage was tabs II, q 4-6h, prn. The nursing staff then assigned a bottle at random from the stock to the patient, and thenceforward, this bottle was used specifically by that patient. The nursing staff then recorded the bottle's code number for that patient. Medication was dispensed when requested for post-partum pain. This was primarily 'after pains', but in a small number of cases consisted of breast pain, episiotomy pain, backache and headache. Patients

*Medications and preparation courtesy Wyeth Laboratories

were interviewed each day as to the type and degree of pain. Degree was graded as mild, moderate or severe. The degree of relief from the medication administered was also ascertained. Relief was graded as complete, greater than 50%, less than 50% or none. Voluntary information was sought as to the occurrence of side effects; but in all cases, information as to the occurrence of any nausea, vomiting, epigastric tenderness, dizziness or drowsiness was specifically elicited. These results were tabulated daily on a form designed specifically for this purpose.

As each patient was assigned her own bottle of medication, she received only one of three possible medications. If a patient had obtained no relief from three consecutive doses of her particular medication, the attending staff was then notified. The patient was then placed on a known analgesic. It was felt that three consecutive doses would satisfy the requirements of the study, and that there was no further need to prolong the patient's pain.

The ambulatory group consisted of patients being seen at two University Student Health Services. Complaints varied. They included myalgia, headache, dysmenorrhea, 'grippe', arthritis and headache. Dosage varied from tabs II, prn to tabe I, q 3 h. These patients were also interviewed as to the same criterias as for the hospitalized group, and the results were tabulated in the same manner. There was one aspect in which this group differed. Inasmuch as total dosage requirement was often obviously less than a complete bottle, full bottles were not prescribed. Thus, it was possible and did occur that

more than one patient could receive a particular medication.

Dundee (24) stated that "measurement of experimental pain is very limited in its clinical applications because of lack of correlation between the findings with various techniques and those obtained with pathological pain." As wide a cross-section of the population and type of pain was sought in order to minimize this type of discrepancy. Interviewing was kept as neutral as possible in order to avoid influencing the patient in any way. Interview technique was preferred as data accumulating method in preference to having the patient record his or her own subjective findings. Wang (68), Free (26), Koteen (42), and Houde (39) have reported that this method of analysis of pain produced by disease concerning 'comfort' after the administration of a medication is the best technique.

DISCUSSION

One of the difficulties encountered in the evaluation of any drug under circumstances such as those of this study is consideration of the effects of the various forces acting upon the patient's subjective awareness of pain and subsequently his response to interview. Modell (49) summarized the forces which may influence data in clinical evaluation, especially when subjective responses were involved. These include: 1. pharmacodynamic action; 2. dosage; 3. choice of subjects; 4. use of controls; 5. collection of data; 6. sensitivity of the method; 7. placebo actions; 8. bias; and 9. forces extraneous to the study.

Pharmacodynamic actions represent the least difficulty in evaluation when objective measurement is feasible. Those which must be measured in terms of subjective response are more difficult to evaluate. This is particularly true in the study of analgesics because pain is so susceptible to suggestion. Drug effect therefore requires careful consideration in relation to the measuring technique. Discrimination in interview must be cautiously exercised. Qualification of the patient's interpretation of degree and relief of pain must be relegated within the potential confines of the pharmacodynamic actions of the drugs in question.

When drug dosage is too low, it will not measure a difference between placebo and active drug (39). Conversely, too large a dose may cause toxicity. The use of a series of graded doses has been shown to provide a more substantial basis for evaluation (36). This

requirement is modified by the flexibility of this type of study. In order for the mechanics of the experiment to fall within the realm of feasibility, dosages must be pre-set so that drugs may be easily prescribed, approach an average clinical dosage, provide enough difference for discrimination and yet be neither too low or too high for the majority of patients.

The choice of subject depends primarily upon the goal of the investigation. Study of the pharmacological properties and activities of a drug is necessary before any evaluation of clinical possibilities is attempted. This is necessary for the establishment of safety, relative toxicity and relative clinical potential of the drug. But carrying this concept one step further, only therapeutic success in the patient with clinical disease can determine its future value. Thus, ultimately study should be carried out in those patients for whom the drug is intended. In addition, it is a basic requirement that the studygroup selected be able as a group to discriminate between active and inert agents. Further, an attempt should be made to select the group by random sampling. That is, it should be as representative as possible of the general population. But again, because of mechanics, some individual selection may be necessary. In this study it was necessary to somewhat limit the range of patients within the hospital setting to parturients in order that an adequate study could be performed within allotted and available time. It is hoped that the group employed reflected a random selection of post-partum patients. The addition of the ambulatory group was an attempt to equate this problem

and thus to achieve an overall satisfactory study.

Knowledge of participation in an experiment, places special subjective pressures on the patient and tends to cause him to act in other than his usual manner. Some patients tend to help the investigator, others react with fear and resentment toward him. For example, in this study, the hospitalized group was readily aware that an experiment was being conducted in regard to its post-partum pain. It became obvious to the interviewer that patients were quick to bring the conversation to the subject of their post-partum complaints, even when questioning was completely neutral or unrelated. Responses were thus obviously shaded or altered depending upon possible desire to please or antagonize. Occasionally a patient would deny pain to the interviewer and yet have requested 'pain pills' on several occasions during the previous day. The reverse condition, patients claiming a considerable degree of pain to the interviewer yet not having requested any analgesic during the previous day, also occurred but less frequently. The ambulatory group was also cognizant of the fact that an experiment was being conducted. But in two areas their attitude may have been altered more toward neutrality. These patients received on the average fewer doses and thus required fewer interviews; and secondly, these patients had very little chance of discussing with fellow patients, as did the hospitalized group, participation in an experiment.

In any event, this awareness alters the subject and thus contributes another facet for evaluation. It would seem that it would be only proper to call upon volunteers (49). In analysis of this possibility,

Lasagna (43) has shown that the volunteer is very infrequently representative of the general population.

No study may be adequately done without the use of controls. The control is the basis for comparison. Not only must it be present, but more significantly it should be sound. One method has been the historical control (49); that is, a recounting of previous personal experience or recorded experience as a basis for comparison. This method is treacherous and rarely justified. The classic experiment uses separate groups for control and treatment. This method requires an extremely large group for statistical significance (50). An alternate method is to give each patient the medication and the placebo serially so that each patient serves as his own control. This may be inappropriate because of progression or regression of pain or disease during the course of the study. Reference has been previously made to the double-blind technique and its method of control.

When the communication of an objective response must be made by the patient to the investigator, considerable difficulty may be encountered in collecting data. The daily report card system (33) was devised in an attempt to overcome the coloring of recollection by intercurrent events. It has been shown to be of no greater practicality than the longer interval system. In general, the data is subjected to the effect of an outside influence on the evaluation by the patient.

Sensitivity of the method is dependent upon the measurement of pain. Pain can be evoked by thermal, electrical, mechanical, chemical

and pathological stimuli. It is a serious error to assume that pain from any origin is equally useful for study of all problems (11). A pain stimulus must be chosen which permits the establishment of a relatively easily perceived end-point.(36). Pain is measured in terms of its relief. For example, an anti-emetic is evaluated by its ability to suppress induced nausea. Hardy (36) has demonstrated the importance of attitude and suggestion in modifying both the experimental pain threshold and the reaction to pain. He reports that pain threshold rises equal to those effected by analgesics can be produced by suggestion through placebos. Even greater rises are produced by distraction.

The usual requirement for "relief" is pain 50% gone at 45 and 90 minutes following drug administration. This relief should persist for 3 hours. It has been stated that patients easily make this discrimination (1). This consciousness to the passage of any certain periods of time was not as easily obtained by this author. This is probably a reflection of the type of patient and the aims of the study. But evaluation of drugs designed to modigy or alter subjective responses arising in pathology must be studied in man himself. Beecher (11) has also shown the ability of postoperative patients to make this necessary discrimination.

The most advantageous area for study of pain and its relief by analgesics is in incompletely or only partially relieved pain as in the patient with chronic pain (malignancy) (24). A statement by the subject is of utmost importance as evidence of the existence of a subjective response or of change in it. However, with the chronic patient,

protraction of only partial relief over a long period of time causes resentment by the patient and results in a loss of cooperation by the patient and by the ward personnel who care for him.

Analgesics exert their effect by altering the individuals response to his reaction to rather than the organic etiology of his pain. This is affected by raising the central pain threshold and not by blocking peripheral stimulation (8). This was demonstrated in a study comparison of wound pain in a group of soldiers and a group of male surgery patients (11). The soldiers had undergone as a group considerably more tissue damage yet, civilian pain was strikingly more frequent and severe than that of the military. This demonstrates that emotion can block pain and its effects must be considered in the sensitivity of the method.

The term placebo has taken on many implications, including a large number of physical and psychic responses to the physician, his ministrations and medications. Reasons for its use can be summarized by indicating its common purposes: as a psychological tool in the therapy of certain mental ailments; as a resource for the weary physician in his treatment of the neurotic patient; to determine the true effects of drugs apart from suggestion in experimental study; and as a device for eliminating bias not only on the part of the patient but also, when used as an unknown (double-blind), of the observer (9). The placebo has also found use as a screening technique for the selection of experimental subjects. In 15 studies involving 1,082 patients,

Lasagna (44) found placebos to have an average effectiveness of 35.5± 2.2%. Not only do placebos produce beneficial results, but they also have associated toxic effects. Nausea 10%, sensation of heaviness 18%, headache 25%, inability to concentrate 15%, drowsiness 50%, fatigue 18% and sleepiness 10% have been reported by Beecher (9). Barber (5) and Beecher (10) have also demonstrated that the placebo is even more effective in the presence of increased stress.

With placebos having a high average effectiveness, clinical impression is a rather nebulous and undependable source of information without the employment of double-blind unknowns, the use of placebos as unknowns and randomization of administration. Other authors add an additional requirement; correlated data (all agents must be studied in the same patient) must be used (10). Free (26) and Zukin (69) disagree with this concept. Free (26) found that the most efficient estimate of drug potency was determinable from the effects of the first drug administered. He found placebo response to be smaller, suggesting that on the first dose patients may have a greater need for relief and thus a greater sense of discrimination. He further pointed out that this made available a greater number of subjects which could be included in any study. Lasagna (44) demonstrated that placebo relief varied inversely to the number of doses given. A 'first dose' technique was applied to this study.

Whenever judgement is an integral component of evaluation of a therapeutic agent, conscious or unconscious bias must be eliminated.

Many times a drug has been praised when its only power was that of the placebo. The physician must also not underestimate the impact of his own interpersonal relationship with the patient and come to believe that his therapeutic successes are always chemical rather than psychodynamic ones. The hopes and the desires of the patient and therapist must be reckoned with in all evaluations regardless of technique. Standard procedure in the avoidance of these errors has been the use of the double-blind technique. But it must be remembered that this does not truly eliminate bias, but only attempts to equalize its effect.

Forces extraneous to the experiment include all the external influences which affect the subject's physical, functional and psychic state. These factors have been purported to be minimized in the hospital environment. And yet, some patients may find this environment disturbing. Randomization of administration tends to equalize the effect of these factors by favoring neither the drug nor the placebo response (49). Still the effects of coincidental environment, family and interpersonal relationships, and emotional stresses or satisfactions are factors which can never fully or properly be weighed.

RESULTS

A total of 206 patients were included in the test for a sum total of 1521 doses. Of these, there were 81 ambulatory patients ranging in age from 16 to 46 years. There were 56 females and 25 males. Table 1 summarizes the results in this group of patients.

TABLE 1

	DEGREE OF RELIEF						
DRUG	SATISFACTORY			UNSATISFACTORY			
	Comp	>50%	%	<50%	None	%	Total
EXPERIMENTAL	7	5	75	2	2	25	16
ASPIRIN	12	7	76	4	2	24	25
PLACEBO	6	17	57+	4	13	42+	40

Only 16 patients or approximately 20% received the experimental drug, in this group of 81. The group was not large enough or varied enough to establish any statistical significance. It is of interest to note that 57% of 40 patients obtained satisfactory relief from placebo. This is far greater than percentages reported by other authors (9, 10, 44). A breakdown of patients by individual complaint is presented in table 2. The occurrence of side reactions was noted in 4 to 16 patients for an incidence of 25%. (See table 4 for a summary of side effects). These were mild and took the form of nausea (1 case), dizziness (1 case) and drowsiness (2 cases).

TABLE 2

COMPLAINT	DEGREE OF RELIEF					
	SATISFACTORY			UNSATISFACTORY		
	Exper.	Aspirin	Placebo	Exper.	Aspirin	Placebo
Trauma	0	1	2	2	2	1
Arthritic	0	1	0	0	0	0
Headache	5	5	13	1	1	7
Grippe	2	5	3	0	0	3
Menstrual	2	4	2	1	3	3
Miscell.	3	3	3	0	0	3

The hospitalized group consisted of 125 female parturients ranging in age from 14 to 44 years. Duration of therapy was 1 to 4 days. Approximately 1083 doses were observed. The number of doses varied from 4 to 20 with 50% of patients receiving 6 or more doses. Satisfactory control of abdominal pain 'afterpain' and a few cases of perineal pain, breast pain, headache, etc., was accomplished in 83.3% of patients. Insignificant untoward reactions consisting of dizziness (2 cases) and drosiness (4 cases) occurred in 6 patients for an approximate incidence of 11%. (See table 4 for summary of side effects).

Table 3 summarizes results in the hospitalized post-partum group.

TABLE 3

	DEGREE OF RELIEF						
	SATISFACTORY			UNSATISFACTORY			
Drug	Comp.	>50%	%	<50%	None	%	Total
Experimental	27	18	83.3	5	4	16.7	54
Aspirin	8	15	74.2	5	3	25.8	31
Placebo	7	4	27.5	9	20	72.5	40

TABLE 4

	EXPER.		ASPIRIN		PLACEBO	
SIDE EFFECT	Amb.	Hosp.	Amb.	Hosp.	Amb.	Hosp.
None	13	48	21	28	35	36
Nausea	1	0	0	0	0	0
Epigastric Distress	0	0	0	0	1	1
Dizziness	1	2	1	0	0	0
Drowsiness	2	4	3	2	2	3

The post-partum hospitalized group data was subjected to statistical analysis for the determination of significance. One of the problems which arose statistically was that under the setup of the study, patients were not selected at random; but the medication which they received was randomly selected by those administering it. This raises

the question of the homogeneity of each sample with regard to the variables of age and whether or not there was equal representation of multiparous and primiparous patients. Past literature has indicated a significant difference in the occurrence of 'afterpains' between these groups (69). It is possible that these variables were fairly equally distributed by the method used. Another consideration is the size of the sample differing from 31 in the smallest, to 54 in the largest.

The question to be determined is how effective is each medication in relation to itself and to the controls when given in a group of 125 postpartum patients for 'afterpains'.

Over one-fourth of the patients obtained relief from the placebo which is comparable to reports previously quoted (9, 44). Approximately 75% of the patients receiving aspirin obtained relief and approximately 83% of patients receiving the experimental combination obtained satisfactory relief.

In considering the results (Table 3), it is obvious that the differences between the three medications are too great to have occurred by chance alone. If our samples are comparable in every other way, we can be reasonably safe in assuming the medications were responsible for this difference. A X^2 test on the data with 2 degrees of freedom equals 30.7 ($p = <.01$).

It is evident that both the experimental drug and aspirin are more effective than placebo, so significance tests with each are not

indicated. The question then arose, " are the differences observed between the experimental drug and aspirin of statistical significance?" In this instance $X^2 = 1.29$ ($p = .3$). This means that in 3 times out of 10 a difference as great or greater than this could occur by chance, so this is not a statistically significant finding.

What must be carefully avoided is deciding that our findings are "not Significant". The data shows that there is a difference in the two groups. Chance could be the reason for the differences as well as similarities, and there could be a "true" difference due to the medication.

In order to establish this determination, another study using a larger sample could be done. Because aspirin is a known effective analgesic, a statistically significant difference between it and the experimental combination might never be attained. But if in successive samples, the experimental combination continued to show a more satisfactory response, we could conclude that there was evidence enough that the drug has merits over aspirin.

It should be noted that great differences were shown in those obtaining complete relief between the experimental combination and aspirin, aspirin and placebo being nearly equal. When considered in the mass of those obtaining satisfactory response little difference is observed. Is there some significance in this difference in the complete relief group? Further investigation of the composition of the group receiving complete relief might shed more light on the matter. Number of

pregnancies or age could be factors as well as simply biological differences in individuals. We can only speculate as to the differences. The tenique itself must be examined as to how clear the distinction was in the interviewer's mind when he assigned a patient to the complete, greater than 50% or less than 50% group.

SUMMARY

1. A short history of anesthesia-analgesia was presented.
2. The pharmacological properties and activities of the drugs involved in the study were described and the findings of other investigators in the field were presented.
3. The method of study, the double-blind technique, was described in detail.
4. A discussion of the factors involved in the experimental study of pain and subjective response to analgesics was presented. Included was a dissertation on the factors of the pharmacodynamic action of the drug, drug dosage, choice of subjects, use of controls, collection of data, sensitivity of the method, placebo actions, bias, and the forces extraneous to the study.
5. From the results, the conclusions were reached that: 1. the number and distribution of the ambulatory patient group were not satisfactory for statistical analysis; 2. a decided difference could be observed in the hospitalized group, but was not statistically significant. The difference between the experimental drug and acetylsalicylic acid could have occurred by chance, but conversely, it could not be discounted that the difference was due to the experimental medication's inherent superiority.
6. A course for further investigation in this was delineated.

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BIBLIOGRAPHY

1. Adrian, E. D., The Physiology of Pain, Practit. 158:76, 1947.

2. Albertson, G. L., Clinical Investigation of Ethoheptazine Citrate and Acetylsalicylic Acid as a Postoperative Analgesic in Oral Surgery, Oral Surg. 12:438, 1959.

3. Alstead, S., Pain and Analgesia: The Philosophic Background, Practit. 184:5, 1960.

4. Barber, T. E., A New Analgesic, Indust. Med. & Surg. 28:54, 1959.

5. Barber, T. E., "Hypnosis", Analgesia and the Placebo Effect, J.A.M.A. 172:680, 1960.

6. Batterman, R. C., Golbey, M., Grossman, A. J., Analgesic Effectiveness of Orally Administered Ethoheptazine in Man, Am. J. Med. Sci. 234:413, 1957.

7. Beecher, H. K., Ford, C., Anesthesia: Fifty Years of Progress, Int. Abstr. Surg. 101:104, 1955.

8. Beecher, H. K., Appraisal of Drugs Intended to Alter Subjective Responses, Symptoms, J.A.M.A. 158:399, 1955.

9. Beecher, H. K., The Powerful Placebo, J.A.M.A. 159:1602, 1955.

10. Beecher, H. K., Enhanced Activity of the Placebo in Stress, Am. J. Physiol. 187:163, 1956.

11. Beecher, H. K., Measurement of Pain: Prototype for Quantitative Study of Subjective Responses, Pharm. Rev. 9:59, 1957.

12. Bender, G. A., A History of Medicine in Pictures, Ther. Notes 68:15, 1961.

13. Berger, F. M., The Pharmacological Properties of 2-methyl-2-n-propyl-1, 3 propanediol carbamate, a New Interneuronal Blocking Agent, J. Pharm. & Exp. Ther. 112:413, 1954.

14. Berger, F. M., Meprobamate: Its Pharmacological Properties and Clinical Uses, Int. Rec. Med. 169:184, 1956.

15. Berger, F. M., The Chemistry and Mode of Action of Tranquilizing Drugs, Ann. N. Y. Acad. Sci. 67:685, 1957.

16. Blumenthal, L. S., Fuchs, M., Meprobamate: An Adjunct to Successful Management of Chronic Headache, Amer. Practit. 9:1121, 1958.

17. Boland, F., The First Anesthesia, Georgia, Univ. of Georgia Press, 1950.

18. Cartwright, F. F., The English Pioneers of Anesthesia, Bristol, Wright & Sons, 1952.

19. Cass, L. J., Frederik, W. S., Bartholomay, A. F., Methods in Evaluating Ethoheptazine and Ethoheptazine Combined with Aspirin, J.A.M.A. 166:1829, 1958.

20. Cobey, C. M., Muscle Relaxants in Management of Orthopedic Back Injury, Amer. Surg. 24:350, 1958.

21. Cooper, C. D., Epstein, J. H., Management of Muscle Spasm Associated with Trauma Resulting from Auto Accidents, Am. J. Med. Sci. 235:448, 1958.

22. Denton, J. E., Beecher, H. K., New Analgesics: Methods in the Clinical Evaluation of New Analgesics, J.A.M.A. 141:1051, 1949.

23. Dixon, N. M., Meprobamate: A Clinical Evaluation, Ann. N. Y. Acad. Sci. 67:772, 1957.

24. Dundee, J. W., A Method for Testing the Efficacy of Oral Analgesics: Its Applications and Limitations, Brit. J. Anaesth. 32:47, 1960.

25. Eddy, N. B., Addiction Liability of Analgesics: Tests and Results, J. Am. Geriat. Soc. 4:177, 1956.

26. Free, S. M. Jr., Peeters, F., Statistical Comparison of Method to Evaluate Analgesics, J. Chronic Dis. 7:379, 1958.

27. Friedman, A. P., Use of Tranquilizers in the Treatment of Headache, Ann. N. Y. Acad. Sci. 67:822, 1957.

28. Gilette, H. E., Relaxant Effects of Meprobamate in Disabilities Resulting from Musculoskeletal and Central Nervous System Disorders, Int. Rec. Med. 164:593, 1956.

29. Glassman, J. M., Letchak, I., Walkenstein, S. S., Seifter, J., Chemical Structure and Action of Meperidine like Analgesics, Am. J. Med. Sci. 230:226, 1955.

30. Glassman, J. M., Seifter, J., Effects of Analgesic Agents on Barbiturate Responses in Mice, J. Pharm & Exp. Ther. 115:21, 1955.

31. Glassman, J. M., Seifter, J., Analgesic Activity of Some Phenylhexamethylenimine Derivatives, J. Pharm. & Exp. Ther. 116:23, 1956.

32. Golbey, M., Leifer, P., Grossman, A. J., Batterman, R. C., Analgesic Effectiveness of Orally Administered Heptacyclzine in Man, Fed. Proc. 15:428, 1956.

33. Greiner, T., Methods of Evaluation of the Effect of Drugs, Am. J. Med. 9:143, 1950.

34. Gross, M., Greenberg, L. A., The Salicylates: A Critical Bibliographical Review, New Haven, Hillhouse Press 1948.

35. Grossman, A. J., Clinical Effectiveness and Safety of a New Series of Analgesic Compounds, J. Am. Geriat. Soc.,4:187, 1956.

36. Hardy, J. D., Wolff, H. G., Goodell, H., Studies on Pain: A New Method for Measuring Pain Thresholds, J. Clin. Invest. 19:649, 1940.

37. Harsha, W. N., A Clinical Study of Meprobamate Used as a Muscle Relaxant Compound, J. Okla. Med. Assn. 53:135, 1960.

38. Haynes, C. E., Morrison, R. D., Clinical Effectiveness of a New Analgesic Combination, J. Mo. Dent. Assn. 37:14, 1957.

39. Houde, R. W., Wallenstein, S. L., Rogers, A., Clinical Pharmacology of Analgesics: A Method for Assaying Analgesic Effect, J. Am. Geriat. Soc. 4:167, 1956.

40. Irby, W. D., Baldwin, K. H., A New Analgesic Combination for Dental Surgery, Dent. Surg. 34:1456, 1958.

41. Keyes, T. E., A History of Surgical Anesthesia, New York, Schumann's, 1945.

42. Koteen, H., Use of a Double-blind Study Investigating the Clinical Merits of a New Tranquilizing Agent, Ann. Int. Med. 49:978, 1957.

43. Lasagna, L., von Felsinger, J. M., Beecher, H. K., Drug Induced Mood Changes in Man, J.A.M.A. 157:1113, 1955.

44. Lasagna, L., Mosteller, F., von Felsinger, J. M., Beecher, H. K., A Study of the Placebo Response, Am. J. Med. 16:770, 1954.

45. Macht, D. I., The History of Opium and Some of its Preparations and Alkaloids, J.A.M.A. 64:477, 1951.

46. McCarty, W. D., Ullery, J. C., Clinical Evaluation of Ethoheptazine in the Management of Postpartum Pain, Postgrad. Med. 26:865, 1959.

47. Minutes of 17th Meeting of the Committee on Drug Addiction and Narcotics, Addendum, 1956, p. 3.

48. Mitchell, E. H., Combined Use of Meprobamate and Aspirin in General Practics, Med. Ann. Dist. Col. 27:190, 1958.

49. Modell, W., Houde, R. W., Factors Influencing Clinical Evaluation of drugs with Special Reference to the Double-blind Technique, J.A.M.A. 167:2190, 1958.

50. Modell, W., Relief of Symptoms, Philadelphia, W. B. Saunders, 1955.

51. Robinson, V., Victory over Pain, New York, Schumann's, 1946.

52. Roden, J. S., Haugen, H. M., Evaluation of a New Analgesic Combination, Missouri Med. 55:128, 1958.

53. Roper, H. K., Man Against Pain: The Epic of Anesthesia, New York, Prentice-Hall, 1945.

54. Seifter, J., Pharmacological Properties of Some Azacycloheptane Analgesics, Fed. Proc. 13:403, 1954.

55. Selling, L. S., Clinical Study of a New Tranquilizing Drug, J.A.M.A. 157:1594, 1955.

56. Smith, P. K., Certain Aspects of the Pharmacology of the Salicylates, Pharm. Rev. 1:353, 1949.

57. Smith, R. I., Miltown in Rheumatic Diseases, Amer. Med. Assn. Meeting, Chicago, 1956.

58. Splitter, S. R., Treatment of Pain in Office Patients with Combined Medication (Equagesic), Current Ther. Res. 2:189, 1960.

59. Sprauer, V. J., Meprobamate in Office Practice, Int. Rec. Med. 171:130, 1958.

60. Symposium: Meprobamate and Other Agents Used in Mental Disturbances, Ann. N. Y. Acad. Sci. 67:671, 1957.

61. Tainter, M. L., Pain, Ann. N. Y. Acad. Sci. 51:3, 1948.

62. Thal, N., Premedication for Electroshock Treatment, Dis. Nerv. Syst. 17:52, 1956.

63. Thomson, T. S., Analgesics, Practit. 184:18, 1960.

64. Tucker, W. I., The Place of Miltown in General Practice, Southern Med. J. 50:1111, 1957.

65. Turvey, S. E., Meprobamate for Relief of Anxiety and Nervous Tension from Various Causes, Canad. Med. Assn. J. 74:863, 1956.

66. Walkenstein, S. S., MacMullen, J. A., Knebel, C., Seifter, J., Metabolic Fate of Hexamethylenimine Analgesics, J. Am. Pharm. Assn. 47:20, 1958.

67. Walkenstein, S. S., Knebel, C., MacMullern, J. A., Seifter, J., The Excretion and Distribution of Meprobamate and its Metabolites, J. Pharm. & Exp. Ther. 4:254, 1958.

68. Wang, R. I., Gruber, C. M. Jr., A Double-blind Method for Evaluating Analgesics in Man, Am. J. Med. Sci. 235:297, 1958.

69. Williams, J. W., Management of Normal Pregnancy, Labor and Puerperium, Obst. & Gynec. 2:423, 1954.

70. Zukin, D., Arnold, D. G., Kessler, C. R., Comparative Effects of Phenaglycodol and Meprobamate on Anxiety Reactions, J. Nerv. & Ment. Dis. 129:193, 1959.