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Classical conditioning of the onset and termination of the asthmatic attack

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CLASSICAL CONDITIONING OF THE ONSET AND TERMINATION OF THE ASTHMATIC ATTACK

by

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I. INTRODUCTION

The relationship of mental life and behavior to health and disease has been discussed by many philosophies and religions and more recently has been approached by the psychological and biological sciences as an area of study.

Evidence from a wide variety of sources has encouraged the notion that an individual's psychophysiological experience plays some sort of role in the etiology of certain physical disorders. This class of disorders, by no means clearly defined, has become known as "psychosomatic" and is defined as a group in which psychic or experiential origins are to some degree causative of demonstrable physical disease. (English and English, 1958)

This dissertation reports an investigation of an aspect of one psychosomatic disorder--asthma. The general method will approach the problem of how the learning process may become involved in and affect the pathological conditions of an internal organ.

More specifically, this study will attempt to demonstrate that previously neutral, non-allergic stimuli can, through experience, acquire the property of both inducing and terminating the asthmatic attack. The method will center around the procedures of classical conditioning.

A major part of the work will involve the development of the necessary equipment and methods.

II. REVIEW OF THE LITERATURE

Asthma Defined

Very few physiological functions have been studied as thoroughly as respiration. This has involved exploration of the peripheral neuromuscular mechanism, the respiratory center potentials, reflex, extrapyramidal, and pyramidal nervous control, chemical control, anatomy, and the physics and chemistry of gaseous exchange.

The clinical picture of asthma is one of labored breathing, wheezing, and production of mucous. Three basic changes underlie this picture. The first is the contraction of the smooth muscle surrounding the bronchioles which restricts movement of the air from the alveoli. With air trapped thusly, the amount of lung volume available for ventilation is reduced. In addition this increased airway resistance necessitates greater respiratory effort to maintain adequate gaseous exchange. This greater effort involves an increase in the intrathoracic pressure which collapses the flexible wall of the lumen and further increases the airway resistance. These factors account for the labored breathing in which the chest musculature and diaphragm work maximally. (Gaensler, E. A., 1961)

Edema of the lung and hypersecretion of mucous both occur during the asthma attack. Peristaltic movements, the action of cilia and coughing assist in further removing this mucous from the lungs. The sound of wheezing may be due partly to the fact of hypersecretion, but Groen (Groen, J.J., 1960) states that the wheezing in asthma may be due to another cause. Noticing how the wheeze can be easily imitated by a normal person and often stopped by encouraging a patient to relax and breathe as easily as possible, he fluoroscoped the behavior of the trachea during wheezing and noticed that both in asthma and during the imitation of the asthmatic wheeze the posterior wall of the lumen collapsed and produced a long stenosis which he felt accounted for the wheeze. This collapse, presumably due to the high intrathoracic pressure mentioned above, was demonstrated to occur experimentally with a post mortem lung when the pressure external to the lumen exceeded the internal pressure.

Asthma, a disorder of respiration, is not completely understood. In an overview, Whittenberger (Whittenberger, J.L., 1951) states, "Without minimizing the importance of psychic, allergic, and other factors operating through the autonomic innervation of the lungs, it can be said that the most serious physiologic defect in asthma must be explained ultimately in terms of the structure and function of the lungs. ...The primary pulmonary feature in asthmatic breathing is, of course, obstruction within the smallest air passages."

Interceptive Conditioning

The present research problem is in an area of classical conditioning which has not been extensively studied in this country. The type of classical conditioning most commonly found in the literature is that in which the conditioned (CS) and unconditioned stimuli (UCS) are applied to the exteroceptors. Such would be the case in eye blink, salivary, and GSR conditioning to shock. The stimuli are apprehended by the external senses.

Other subclasses of classical conditioning have been recently outlined by Razran (1961). The bases for his classification are: 1. whether the CS acts directly on an extero- or interoceptor, 2. whether the UCS acts directly on an extero- or interoceptor, 3. whether the response is visceral, skeletal, or sensory-verbal (report of sensation). Types of conditioning resulting from the different combinations of these classes, according to all indications, have their own properties of speed of formation, stability, role of conscious factors, etc.

In the above article Razran induces what the properties of these different classes of conditioning may be. What could be predicted concerning the possible outcome of the present work? First it is necessary to describe this experiment in his system. Since bronchospasm of the lung will be the principle response worked with, the conditioning is visceral. The lungs will be stimulated directly by chemical means (described fully in a later section), while the CS, a tone or light, will involve an external sense. The full classification is therefore *visceral extero-ceptive conditioning*. Razran indicates that this type of conditioning is probably slower to form but more permanent than the more common extero-exteroceptive conditioning exemplified by salivary conditioning. He describes one experiment with 6 sheep in which stimulation applied to the reticulum produced an unconditional change in the rate of contractions in the rumen and rectum. Conditioning this change to the sound of a bell required 8-13 trials for appearance and 16-24 for stabilization. It is, however, impossible to predict from such studies what should be expected in the present work which uses a different organism and different stimuli and responses.

General coverage of Russian work in the field of "interoceptive conditioning" (a term used loosely to describe conditioning of the behavior of internal organs) can be found in two books (Brazier 1959, Bykov-Gantt 1957). Russian work comprises the largest body of literature currently available. Successful conditioning of the behavior of a number of internal organs has been reported as well as changes in the blood--clotting time, leucocyte count, sugar level, etc. It is probable that conditioning involving the interoceptors plays an important role in the regulation of bodily processes. The relationship between classical conditioning and emotions is discussed recently by Mowrer (1960).

With the completion of this general introduction to interoceptive conditioning (which should place it within the broader field of classical conditioning) the writer will now proceed to examine in detail the conditioning literature in the field of asthma and some general work in the field of respiration.

Conditioning, Respiration, and Asthma

In a lengthy article, Freedman (1951) summarizes much of the work relevant to respiratory conditioning done principally in Western countries. He points out that conditioning of respiratory change in guinea pigs was obtained by Upton in 1929 by pairing electric shock to the hind limbs with a tone for several hundred trials. In the early trials the CR was not at all the same as the UCR and consisted of an evening out of the respiratory pattern rather than a sharp inspiration. Freedman feels that an unconditioned effect of the tone may have contributed to this result--that is, that the evening out of the respiration was not a CR but an UCR.

Horton (1933) used an electric shock which was presented during the last few seconds of a 10-second tone. He found that the CR was again a general inhibitory effect rather than hyperpneic. And again, the question must be raised as to whether this is a genuine CR, or if this should be analyzed as a case of delayed conditioning in which no CR was established. Although Pavlov commonly used an interval of 30 seconds between CS and UCS and referred to longer periods as delayed conditioning (Brogden 1951), the different nature of respiratory conditioning might make this interval of 10 seconds too long. The regularization in breathing obtained in both of the above experiments may be part of the investigatory reflex which would be maintained by succeeding shock. Pavlov comments on this relationship as follows: "We already know that every new stimulus which evokes the investigatory reflex ceases on repetition to have any effect unless the stimulus has been followed up with some other reflex." (Pavlov 1927, p. 385)

Kappauf and Schlossberg (1937) throw more light on the problem. In conditioning sharp inspirations in the white rat with shock and buzz, they found that CS-UCS intervals between 2/3" and 1" were optimal, but that generalized changes in respiration did not have such a specific time period, with periods from 1" to 7" being equally effective. They attribute the first result to "the waning effect of the long buzz." Interestingly enough, however, under strong shock conditions, the differential effect of the intervals dropped out.

Again, however, it will be difficult to compare results of conditioned gasps with asthma which is a more autonomic phenomenon. Lacey (1961) and Razran (1961) feel that for asthma conditioning the latency between the CS-UCS should not be critical since it does not appear to be in interoceptive conditioning.

Walker and Kellogg (1939) using a buzzer followed by electric shock found that respiratory CRs of a decrease in amplitude were established in half the number of trials as were conditioned flexions of the leg, and far outlasted the flexion during extinction. This same finding regarding the rate of formation and extinction has often been informally reported by authors interested in other responses.

Polypnea in humans, produced by an electric shock to the hand, was conditioned by Finkelstein, Alpern and Gantt (1945). Changes in rate were also seen to occur in humans who were asked to recall a painful stimulus (Finesinger and Mazick, 1940). The effectiveness of a verbal substitute for the conditional stimulus has often been found in classical conditioning studies.

Freedman (1951) cites an experiment which used food as an UCS and was able to condition very slight increases in rate of respiration which outlasted salivary conditioning. He also summarizes several experiments in which respiratory changes occurred in conjunction with a conditioned conflict situation. An approach-avoidance conflict was commonly induced by punishing an animal in association with its feeding situation. Dyspnea and polynea were produced in very few trials. The study most relevant to asthma is the one done by Gantt (1944) who kept his dog "Nick" for 15 years with an induced neurosis, and observed polypnea, pseudo-asthmatic respiration, inspiratory gasps and staircase expiration as one of four types of disordered respiration. Its similarity to asthma was observed, but it was never shown to be really asthma. No musical rales were found in the lungs as in human asthma.

In summary thus far, it is seen that respiration is relatively easily affected in the classical conditioning situation in which pain produced by an electric shock is present. One experiment using food is reported. In most cases where respiratory conditioning has occurred incidental to some other response, it has generally formed sooner and been more resistant to extinction.

The above experiments can be divided into two general classes--those which produce a change in respiration by a direct conditioning procedure, and those in which a change in respiration occurs as a result of a conditioned conflict situation. The former experiments generally have worked with a gasping response which is successfully conditioned using a CS-UCS latency of about 1 second. With longer times the response to the CS consists of a regularization of rate and amplitude which often is the unconditioned respiratory response to the presentation of a sound.

The studies which have attempted to condition actual bronchospasm are recent and few in number. In part this is because they had to await advances in conditioning techniques, an increase in the understanding of asthma and the discovery and development of unconditional stimuli which would evoke bronchospasm. For this latter purpose methods have been worked out for the development of pollen extracts and the use of histamine and acetylbetamethacholine chloride.

Herxheimer (1953), working with aerosolled allergens, found that after placing a person in a situation in which he had previously experienced asthma, he would often develop the signs and symptoms of asthma. Unfortunately, details of this phenomenon are incompletely reported since it was not Herxheimer's principal interest. It was, however, his apparatus for the presentation of aerosols which served as the basis for the apparatus used in this study. This is described in a later section.

The following study did not attempt to condition asthma, but attempted to evoke asthma with non-allergic stimuli found from a patient's history to have been evocative of asthma in the past. (Dekker and Groen, 1956) Their purpose was to demonstrate in the laboratory an actual attack of asthma that could be shown to be triggered by a stimulus in which the chemistry of allergy would not be present. It was assumed that some sort of conditioning mechanism might explain their positive results.

In essence this was an attempt to produce the "paper rose" effect. This is a phenomenon reported in the allergy literature in which a patient allergic to roses reacts also to paper roses. This experiment differs from the usual anecdoted report in that measures of the vital capacity were taken as a quantitive dependent variable. Their method was to take a baseline of three vital capacities, then present the "emotional stimulus." Vital capacities were taken every four minutes, and results were considered positive if the vital capacity fell more than 10% of the average of the first three baseline vital capacities (providing the drop was progressively moving in one direction and therefore did not appear to be random). Examples of stimuli adjudged important on the basis of the individual patient's history were: riding in an elevator, seeing a goldfish, seeing a picture of a horse (in a S sensitive to horse dander), etc.

The results of the experiment were as follows. With a total of 12 Ss, 6 showed no change in the vital capacity on presentation of the emotional stimulus. Four of these 6 stated that the conditions surrounding the presentation did not closely resemble the situations in which their attacks actually occurred. Three Ss showed "transient" decreases in vital capacity (only two values are reported and are 17% and 21%) with slight signs of asthma. The remaining three Ss showed marked clinical asthma, one attack of which had to be terminated with an injection. Furthermore, the provoked attacks were generally found to be reproducible. From the interview material, fantasies and dreams reported in relation to the stimulus it became apparent that, as the authors observed, the stimulus had in some way been associated with traumatic life experiences in which a great deal of emotion was involved. That is, the patient would recall an emotionally charged situation in which the stimulus object played some role. In the instances reported, however, the recalled traumatic experiences had <u>not</u> been accompanied by asthma! For example Pt. L. (p. 62) told the authors she got asthma from looking at a goldfish. In the first experiment she was presented with a goldfish in a bowl in the laboratory and developed severe asthma which subsided after the fish was taken from the room. In the second experiment she was presented with an obviously fake goldfish in a bowl and had another attack. She then told of a dream she had following the first experiment involving falling into a goldfish bowl and suffocating. She awakened from this dream in asthma. Thus, both the goldfish and its image in the manifest content of the dream were in each case followed by asthma.

The important feature here is that no asthma is reported to have occurred at the time of the original incident with the goldfish. From the point of view of conditioning theory then, why the goldfish should trigger an attack of asthma is open to question. There is, however, an experiment with salivary conditioning which indicates that the unconditioned response may not be necessary for conditioning to occur (Crisler, 1930). In that experiment, salivation was blocked during the conditioning trials by atropine. Morgan (1951) concludes from this and a similar experiment, "These experiments, involving the artificial blocking of the motor response, show clearly that response need not occur in order for learning to take place. The parts necessary for learning, therefore, lie upstream from the muscles or glands involved in the execution of the learned response."

In Dekker and Groen's third experiment with patient L, the bowl alone provoked asthma. During this experiment, the investigator threw the bowl to the floor in "an effort to break through the patient's reaction." This was followed by a further increase in dyspnea and the comment, "That is exactly what my mother did, she threw the bowl into pieces into the dustbin." (Dekker and Groen, 1956, p. 64)

The authors state that it is not strong emotion alone which is evocative of the asthma since many of the associations of the patient given during an extended baseline period were highly emotional but did not affect the vital capacity as did the presentation of the stimulus.

The authors were attempting to produce reliable psychogenic asthma in the laboratory. They found that even though the patients realized the artificiality of the situation they often seemed to be powerless to stop an attack from developing. Without drawing conclusions about how the stimuli acquired the property of eliciting the asthma, the authors felt that the specificity of the stimulus, and its reliable and seemingly compelling action were in line with what one would expect through the process of acquired conditioning.

Unfortunately, this experiment omits mention of what the S's instructions were. From the material presented it seems that the Ss must have known the purpose which, then, opens the way for suggestion, facilitation, and/or other factors to operate.

The question has here been raised how conditioning could have occurred. For conditioning to have occurred in the usual manner, there must be an association of the UCS-UCR and some previously ineffective stimulus. If in the traumatic, i.e. highly emotional, situations recalled by the patients the UCR (asthma) did not occur, how is one to later understand the action of the psychogenic stimulus? In addition to material already cited it is possible that the memory was not that of the actual conditioning process. This is possible since in another patient (Pt. M.), who also had asthma triggered by the sight of a goldfish, the previously unremembered first attack occurred when her husband, a butcher, made her clean up some calf blood. In this patient, as in Pt. L., the goldfish was connected with the idea of being trapped or suffocated.

Although this type of experiment cannot be used as evidence for conditioning it does indicate that if a conditioning process is involved it is complex, possibly involving generalization mediated by meaning. The common mediating response in cases L and M might be the idea of suffocation, being trapped, or oppressed. This would mean that any stimuli rendered equal by a common meaning of "being suffocated" should tend to produce the response of asthma.

The next experiment to be reported involves the direct attempt to produce human conditioned asthma in the laboratory. (Dekker, Pelser, Groen, 1957) They use two Ss to attempt to condition the onset of asthma. A brief quote from their summary will be followed by a careful examination of their methods.

> ...two asthmatic patients who had positive skin reactions to grass pollen and house dust respectively and who reacted by typical attacks of asthma when they were given these allergens to inhale in the laboratory. The inhalation of the neutral solvent of the allergen extracts initially caused no reaction.
>
> In the course of further inhalation experiments, however, the reaction patterns of the patients changed. They began to react also to the inhalation of the indifferent solvent with attacks of dyspnoea. Later it was found that the inhalation of pure oxygen in the laboratory caused attacks of asthma, and finally it was sufficient to introduce the mouthpiece of the apparatus or to imitate a connection of the mouthpiece with the inhalation apparatus, to provoke severe paroxysms of asthma. These attacks, once developed, could not be distinguished from those which appeared after inhalation of allergens or from spontaneous attacks:

> more specifically they reacted favourable to inhalation of isoprenaline or injection of Multergan.
>
> These observations gave the impression that the patients had become conditioned by the allergic attacks to the inhalation situation and later even to certain "fragments" thereof. (p. 101)

In this experiment the S is seated in front of a spirograph with which he takes a vital capacity every four minutes. Again, whatever instructions were given to the Ss are not reported, but the authors mention that this same apparatus and procedure was used to test for allergies in a number of patients and that "conditioned" phenomena appeared only in these two Ss. Whether these two Ss were preselected for a conditioning experiment or whether they are two who happened to show this phenomena when being tested is not explained.

A modified Herxheimer apparatus is used and the UCS in the nebulizers are grass pollen extract and house dust extract. Details of construction are presented, and the same criteria of an asthmatic attack are used as in the previous article: a 10% reduction from the baseline of the vital capacity. The S is evidently able to see the full operation of the equipment and the operator of the equipment is right in the room with the S. The only thing the S does not know, apparently, is the identity of the chemicals in the nebulizers.

The results with both Ss are presented in detail. It is noteworthy that the degree of asthma produced by the UCS involves a drop in the vital capacity of between 40 and 60%. This is dramatic conscious asthma, and the S must have been well aware of what was going on, especially since he was given isoprenaline inhalations or intramuscular thiazinamine to end the attacks. The importance of this fact lies in the demonstrated facilitation of conditioned response formation by the proper instructions to the S, and the relatively unknown role of the effects of conscious expectation. (Hilgard, 1951)

No CS was presented other than the stimuli involved in the conditioning situation itself. This includes the experimenter, room, equipment, and the acts preceding inhalation, especially that of placing the glass tube in the Ss mouth. It is the latter which the authors felt became important.

The first S, Mrs. A., in her first session for adaptation to the apparatus and demonstration of the neutrality of the CS showed a drop of 11% below the baseline with slight dyspnea. She was then given reassurance and the vital capacity rose. The CS appeared to be neutral during the second session, so a conditioning trial was given. In the third session, the CS was neutral in an extinction trial and another conditioning trial was held. Conditioning was done for sessions four and five, then during the sixth session another extinction trial was held which produced a drop of 11% after 10 minutes. This long latency of response is interesting and would be important to compare with the drop produced in the very first session when the CS was not found to be originally neutral. If the latency was radically different (longer or shorter) it would be evidence that this second drop was not the same unconditioned response to the situation which in previous trials had been temporarily inhibited. Such inhibition could have been produced by the E's behavior and assurances given the S.

Only a few more conditioning trials were given, and some half dozen extinction trials were done. All were positive. In each extinction trial the equipment was checked to eliminate the possibility of allergens, and finally it was seen that even when the tube was disconnected from the apparatus and a different E was present, a drop of 46% was produced.

If this procedure represents pure conditioning, it apparently occurred after two conditioning trials in which drops of 54% and 40% respectively were produced. The amplitude of the CR increased later in the series as more conditioning trials were given.

The second S, Mrs. B, was subjected to a similar procedure. In this case, an inhalation of neutral solvent produced a drop of 9% in the original test. Following two conditioning trials with drops of 12 and 59%, a first extinction trial produced a drop of 40%. After several more trials, the S's seating herself in front of the atomizer box was sufficient to produce a drop of 23%. Conditioning apparently occurred in two trials.

The spacing of trials for these two Ss was as follows:

Pt. A.: Every one or two days. Maximum time between trials: 5 days.
Pt. B.: One trial per week.

The authors feel that case B is the weaker evidence of the two since this S had difficulty giving reliable vital capacities and also used a great deal of hand-atomized "respifral" outside the conditioning situation. But they feel that the regularity of the drop following the inhalation situation made assumption of a causal relationship reasonable.

The experimenters then attempted a series of counterconditioning trials, group therapy, suggestion, persuasion, reassurance, and explanation of the experimental procedure in order to eliminate the asthmatic response to the glass tube. The counterconditioning procedure, injecting zinamine immediately prior to placing the tube in the S's mouth, seemed to work in Pt. A., but the asthmatic response was reestablished in a single trial. In Pt. B. the same results were obtained, but the entire procedure was stopped for 11 months in which S was in group therapy. This effected a change in her personality which rendered her less withdrawn, shy, and oversensitive.* When she returned to the inhalation situation she had a great many unconditioned attacks provoked during a series aimed at desensitizing her allergy to house dust. During this series the CR phenomenon could not be elicited. The authors feel:

> Apparently the "preparedness" of the patient to become conditioned by the experience of attacks in the laboratory situation had become much less. It was surmised that this change in "conditioning behavior" was related to her changed attitude to the doctors and the laboratory situation in general, but this could not be proven. (*Ibid*, p. 104)

The attitude of both patients toward the test procedure is described as "fearful" and a change in this attitude apparently occurred in patient B prior to the second series of conditioning trials.

Other work using a model of conditioning theory has been done by C. Michalova (1960) at the Institute of Industrial Hygiene and Occupational Diseases of the Prague Department of Pathophysiology. Of relevance to this paper is both the theory (discussed later) and the one attempt reported to associate the odor of menthol with the action of adrenaline on the asthmatic state. This is, of course, quite a different procedure than other research summarized in this section which attempted to condition the *onset* of

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* Work relating emotion and conditioning is discussed in final section of this paper.

asthma.

Her procedure and results are summarized in the following quotation.

> In the first few days adrenaline is given alone after approximately 10-20 injections it is generally possible to use a conditioned stimulus. The strongest stimulus is the injection procedure so that any indifferent sterile solution injected subcutaneously can be used. ...As a weaker conditioning factor we use an olfactory stimulus (a weak menthol solution or others). After each injection the patient is left at rest for half an hour inhaling the menthol solution from a piece of gauze. The effects of the conditioned stimulus are evident during an attack and in the presence of dyspnea. But even during an intermission, it is generally possible to demonstrate the release of latent spasm spirometrically or by an other objective method. Chvapil...proved also a conditioned decrease of eosinophiles in our patients.
>
> According to the intensity of the conditioned association and the general state of the patient the injection of adrenaline is gradually more frequently alternated with the injection of the indifferent solution or the inhalation of the menthol solution alone. ...with the help of this inhalation they sometimes succeed in suppressing a slight attack of asthma.

Unfortunately, there is little quantitative specification of variables. Of interest is the overlap of one half hour of the conditioned stimulus and the UCR, a time relatively common in interoceptive conditioning and unheard of in exteroceptive conditioning.

The guinea pig has been selected as the best laboratory animal for research into asthma conditioning for two reasons. First, sensitivity to foreign protein can be induced relatively easily (anaphylaxis). Second, the anaphylactic reaction occurs principally in the lungs and it is both this locus and the nature of the reaction that a number of authors find similar to the phenomena of human bronchial asthma. This first article (Noelpp-Eschenhagen, 1954) contains many basic references describing the nature of the anaphalactic reaction.

The conditioning work involved various conditioned stimuli and two asthmogenic agents (histamine and antigen). The general procedure was similar to that in the human conditioning experiments and consisted of placing the animal in a standard box into which sprays of the UCS could be introduced. After asthma was fully developed, the conditioned stimulus was given for about 10 minutes. Five conditioning trials were followed by the first extinction trial which consisted of presenting the CS, sometimes with and sometimes without the sound of the nebulizer. The general results are summarized as follows:

> In a relatively high percentage of the animals, asthma-like reactions were obtained as conditioned reflexes. A relatively small number of training exposures (5 to 10) was sufficient to produce significant effects, provided the exposures followed on consecutive days. As shown...the reactions obtained do not represent the fully developed prototype of severe asthma. Some characteristics of the earlier stages of an attack, however, can be distinctly recognised: increased frequency and amplitude of breathing, slightly prolonged expiration and the broken course of the expiratory side of the tracings. According to Gantt "conditioning is a selective process rather than a duplication *in toto*" so that the conditioned response to an agent may only consist of a part of

> the original conditioned reaction varying qualitatively as well as quantitatively. Reflex reactions persist as long as the signal lasts and stop abruptly as soon as it is withdrawn. The reaction may be reproduced up to 5 times, provided suitable time intervals be allowed, but in agreement with Pavlov's observations, it tends to become exhausted. (p. 384)

Inspection of the graphs reproduced in the above article show, indeed, that the change in breathing as measured by a thoracogram and abdominogram does occur <u>immediately</u> on presentation of either or both of the conditional stimuli. There is so slight a latency that it is virtually imperceptible. Now, as discussed elsewhere in this paper, one of the lesions assumed to be fundamental in the disorder of asthma is the bronchoconstriction produced by contraction of the smooth muscle in the bronchi. Presumably, if this were conditioned there should be some reasonable latency involved in both the constriction and relaxation of the muscle. No latency occurs, however, and this fact alone casts doubt on any involvement of the smooth muscle and autonomic nervous system. The speed of the changes is like that observed in the current work when some novel stimulus is introduced into the experimental room which houses the human S. The nature of response to a sound was different, usually consisting of a <u>reduction</u> in amplitude and a <u>regularization</u> of rate. In Noelpp-Eschenhagen's work the result is the opposite and is representative of the type of breathing seen in guinea pig anaphylactic asthma according to the authors. Their caption under the figure showing this breathing is "asthma-like breathing as a conditioned reflex." No mention is made of the presence of wheezing.

It almost seems that the change in breathing reported is similar to the rat studies previously reported. It can be looked on as an expectancy-attention response. The difference between the rats (regularization and reduction of tidal volume) and the guinea pig (irregularity with increased rate and volume) could be species differences as well as different unconditioned stimuli (electric shock and anaphylaxis, respectively).

Also reported is what the authors refer to as their only case of "spontaneous conditioning." An animal which had had several conditioning trials developed "severe asthma" on being placed in the apparatus. This is important since it relates both to the next experiment and the present work. What they refer to as "spontaneous conditioning" appears to be ordinary conditioning with the box and equipment as the conditioned stimuli.

Another part of their research tested Selye's (1950) hypothesis which states that exposure to a stress situation facilitates development and increases the persistency of conditioned reflexes. Two groups of 14 rats were given the same conditioning treatment as described above. One of these groups was a control, the other was, prior to conditioning, exposed to the stress of a brilliant flashing light for several weeks. A number of signs of stress were observed in the animals. In the conditioning trials all 14 stressed animals showed the conditioned breathing phenomenon as compared to 5 definite and 4 equivocal reactions in the control group.

Irregular spacing of conditioning trials showed very ineffective results.

Finally, the authors investigated the effect of administration of small doses of ACTH or cortisone on their histamine and antigen-induced asthma. Their conclusions were that ACTH medication does not have any significant effect on either.

One other study of conditioned anaphylactic asthma in guinea pigs is reported in the literature by Ottenberg, (Ottenberg, et al, 1958). As in the Noelpp study, an egg white spray was used as the UCS after the requisite sensitization to the egg white had taken place. The animals were placed alone into the conditioning chamber into which, after a minute of observation, the spray was introduced. From an original group of 30 animals, 6 animals were selected who had attacks in 10 or more consecutive conditioning trials. These animals were given a series of consecutive extinction trials until no asthma was present for 5 consecutive trials. The results of the extinction trials are as follows (p. 397-8):

> During the extinction phase all of these...6 animals had asthmatic attacks without the presence of egg white spray. Four animals continued to have attacks through 9 trials. The attacks were milder and did not progress to convulsive trembling or seizures. ...the extinction curve for the animals follows a typical extinction pattern in response to a learned stimulus. Extinction was apparent in all after 13 trials. This we define as learned asthma.

The main criticism of this work must center around the criteria of asthma which consisted of an observer's report of use of accessory muscles, gasping, coughing, and pronounced respiratory distress. A recent visitor to the laboratories where the work was done found that when more precise measures were used (airway resistance, breathing pattern) there have been up to 75 conditioning trials with no sign of conditioning. (Luminet, 1961) Although this latter report is necessarily incomplete, the experience gained in the present work indicates that wheezing is not a good measure of asthma. For example, in the human Ss used, severe asthma has appeared without wheezing and there has been wheezing during mild asthma. As pointed out before, wheezing can also be imitated at will by humans, and need not represent true interoceptive conditioning of the internal organ.

Summary of the Literature

Research attempting to produce conditioned changes in respiration was summarized. Two general methods were noted--changes produced as a correlate of a behavioral conflict situation, and those produced in a direct attempt classical conditioning situation, commonly using electric shock as an unconditional stimulus.

Among the animal asthma studies the Noelpp experiment differs from the others in applying the CS after the asthma response is well developed. In such a case, the CS could not serve as a warning signal. The effect of the CS differed from that in the rat experiments in which the CS provided a several seconds warning for the onset of painful shock.. Several possible explanations were offered for this difference.

One study attempted to condition the termination of asthma in humans. Lack of quantification and precise reporting make this study difficult to evaluate.

Regardless of the nature of the response to be conditioned in the above experiments, there was considerable difference between organisms of the same species in their conditionability. There is some evidence that conditionability (if, in fact there is a general factor of conditionability) changes from time to time in the same organism and that one difference may be the degree to which the organism has been stressed. If one may regard psychotherapy as a method for reducing needless stresses on an organism, the change in Dekker, Pelser, and Groen's second patient following therapy would have been expected.

Perhaps the best evidence for possible conditioning of human bronchial asthma lies in this latter experiment.

It used allergen-evoked asthma, and does not require comparison with lower species or with the anaphylactic reaction. Unfortunately, there were many uncontrolled variables, discussed above, which can provide alternate explanations of the results.

A clear demonstration of bronchospasm conditioning has not been reported.

III. EXPERIMENTAL DESIGN

This research used human subjects and attempted to condition two different responses to exteroceptive stimuli. The first response was the onset of asthmatic bronchospasm, the second was the termination of the spasm. This study attempted to avoid the criticisms made of previous work by: 1) keeping the purpose of the study unknown to the subjects, 2) reducing experimenter-subject contact and the possibility of suggestion, 3) obtaining several measures of the asthmatic state, 4) gathering as much information as possible for _ex post facto_ analysis, and 5) a tangential purpose of gathering material which can be used in other studies.

In order to achieve the above aims, a major function of the work was the development of equipment and techniques.

The general design was non-analytical (Underwood 1957), p. 273). That is, it did not undertake the systematic analysis of relevant variables. This was due to two factors: the exploratory nature of the work, and the small number of subjects available. It meant, too, that a control group could not be used to guard against pseudo-conditioning. There is nothing, however, to prevent this control from being added later if it seems warranted. The first task was to establish the existence of some phenomenon which might be due either to conditioning or pseudo-conditioning, and the aim was to maximize the chances of demonstrating this phenomenon in as many Ss as possible.

The proposition tested is a particular, existential one (Cohen and Nagle 1934, pp. 36-42), not a universal. The proposition is that some asthmatics' attacks are conditioned responses, and this implies another--that some asthmatics are conditionable. According to the above reference, this is interpreted to assert that: There is an asthmatic whose asthmatic attack is conditionable. Unfortunately this cannot be disproved without testing all asthmatics under all conditions. It could, however, be supported by the finding that a single case has this property. Thus no statistical method is required to establish the truth of the above--that is, there is no requirement that a "significant" number of subjects show this phenomenon. There can only be the question of whether the change in the dependent variables in any given case is sufficiently significant to indicate that conditioned asthma has, in fact, occurred.

In accordance with the foregoing, all Ss received the same treatment, subject to changes required by practical considerations and ethical principles. Essentially, there were three types of trials: adaptation to the apparatus, conditioning, and extinction. A rigid schedule of conditioning and extinction trials for all Ss was impossible because of the fluctuations in the degree of asthma, the different spacing of trials, interruptions due to various causes, and the S's cooperation.

A conditioning trial consisted of a temporal association of a tone or light with the onset of artificially induced asthma, and the association of a different tone with the artificial relief of that asthma. The most common pattern was to attempt three or four conditioning trials, then try an extinction trial. Usually, in an extinction trial, both conditioned stimuli would be tested.

IV. RELEVANT VARIABLES

Independent

Trials/day: Because of the exertion required of the S in the course of a single trial, these were generally kept to one trial/day. In one S, Mrs. G., who had to come a great distance, two trials/day separated by about an hour and a half were used.

Trials/week: Most Ss imposed a limit here based on their available time. The most common pattern was 3/week.

Conditional stimuli: The selection of the two tones was made on the basis of the frequency of their use in general psychological conditioning experiments. Volumes represented the moderate level found by most investigators to be efficacious for conditioning. Six judges were used to determine that the volume of the tone was clearly audible but not sufficient to provoke any strong reactions. For several Ss in whom the thousand cycle tone (henceforth abbreviated CS_{1000}) had not yet been associated with asthma, the oscillating light (abbreviated CS_{OL}) was used. to facilitate discrimination.

Unconditioned stimuli: For the production of an asthma-like state in human asthmatics, one has the choice of histamine, aerosoled allergens, or acetyl-beta-methacholine chloride. The latter was chosen because it produces relatively mild, short-lived attacks, without having a taste or particular sensation when inhaled. In the present apparatus, concentrations of 1:500, and 1:100 were used.

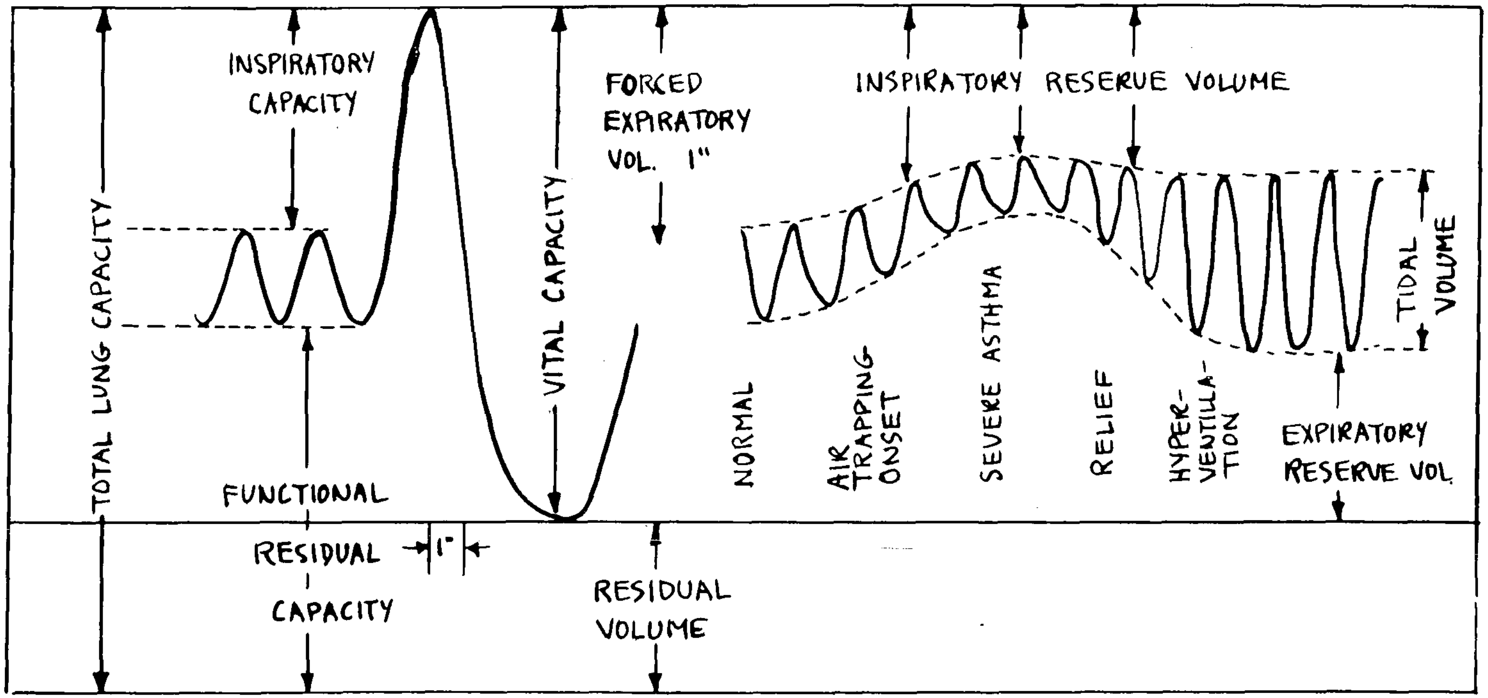
For the termination of the attack, Isuprel was used in concentrations of 1:200 and 1:100. It relieved induced attacks promptly. In larger doses, however, it had the one disadvantage of producing sensations of heart pounding and general bodily acceleration common with sympathomimetic drugs.

CS-UCS delay: The critical duration of this period in eyeblink conditioning apparently does not hold for autonomic conditioning since in the vast Russian research literature in this area, all kinds of time relationships are observed. Dr. John Lacey (Lacey 1961) felt that no precise time relationship would be necessary outside, of course, of the general requirement that the conditional stimulus precede the onset of the UCS. (The actual time relationships used are described under "procedure.")

Dependent Variables

A number of variables can be used to diagnose the presence of asthma. These are described below, and the principle ones are diagrammed in Fig. 1.

Vital Capacity: the maximum amount of air which can be exhaled, this is a standard test for pulmonary disorder. In asthma, this measure is reduced by a



COMMON TERMS USED IN PULMONARY FUNCTION TESTS.

SCHEMATIC DRAWING OF RESPIRATION DURING ONSET AND RELIEF OF MECHOLYL- ASTHMA

[READ LEFT TO RIGHT]

ADAPTED FROM PAPPENHEIMER (1950)

Figure 1

Illustration of respiratory variables.
Read left to right. Inhalation: upwards.

contraction of the smooth muscle sufficient to prevent air from passing from the alveoli.

Expiratory rate: The rate at which air can be exhaled during a maximum expiratory effort is expressed in ml/sec. Partial obstruction of the air passages found during bronchoconstriction reduces the rate of air flow. Rates for each of the first three seconds were measured.

Air Trapping: During the onset of asthma, since the mechanics of breathing facilitate inspiration more than expiration, each respiratory cycle increases the expiratory reserve volume. This volume becomes larger and larger and appears as shown in Fig. 1.

Wheezing: Wheezing was detected by a microphone placed over the trachea. Recording of breathing sounds for all sessions was not practical, so ratings of wheezing sounds were made on the following four-point scale by two observers.

1. No audible sounds
2. Slight wheezing
3. Moderate wheezing
4. Heavy, labored wheezing

Interviews: These were used for data on S's awareness of external stimulation and sensations of respiratory difficulty. This data was collected for its possible value in an *ex post facto* analysis, and was not intended for use as a measure of asthma. These interviews were given following each experimental session.

V. THE DESIGN OF EQUIPMENT

For the experiment two adjacent rooms were available, one for the S, the other for the equipment and experimenter. A one-way screen permitted a view of the S, while a two-way sound system permitted both communication and the recording of interviews. The conditioning stimuli (the 1000 and 400 cycle tones) were introduced into the S's room over this same system. The S's loud-speaker was located to the right and slightly behind him.

An effort was made to have the S's room be a constant, unvarying environment, affectively neutral, comfortable, soundproof, and relatively unvarying in temperature. These qualifications were generally met. To a person sitting in the room the only audible sound was the drone of the air exhaust fan which successfully masked all but the loudest sounds from the outside. The off-white room, relatively plain and undecorated, contained a desk and chair. Along its wall hung the experimental apparatus seen by the S: a microphone, wrist electrodes, and breathing tube. The room was evenly lit by two 250 watt bulbs aimed at the ceiling.

In the control room, the equipment consisted of two principal parts: that for the recording of respiratory variables and that for recording heart rate. In addition there were lesser systems for signalling the S when it was time to give a vital capacity (a ten second duration light in the S's room), for monitoring wheezing, and for recording the time of experimental events such as the application of the various conditional and unconditional stimuli.

In the heartrate system the principal piece of equipment was a Grass EEG-EKG-EMG eight channel recorder. Two channels were used to record the heartrate at different amplification from two electrodes, one on each wrist. A third channel recorded the time of application of the UCS while the fourth recorded the CS and a six second time blip which facilitated analysis of the record.

The major equipment used for recording respiratory variables was a modification of the Herxheimer (Herxheimer, 1951) apparatus. In brief, this is a device which gives a spirogram of the S's breathing including his vital capacities, and at the same time allows nebulized substances to be introduced into the breathing circuit. This consists of a closed breathing circuit using forced air circulation into which, from a side circuit, nebulized bronchoconstrictor (Mecholyl) and bronchodilator (Isuprel) could be introduced. The continuous respiratory tracing is obtained by a Collins nine liter respirometer. Recording was done on a rotating kymograph drum with a 6 volt current burning a tracing on "teledeltos" paper. The Kymograph used an extension arm of about four feet in length so that the Ss breathing record would be visible to E (Fig. 2).

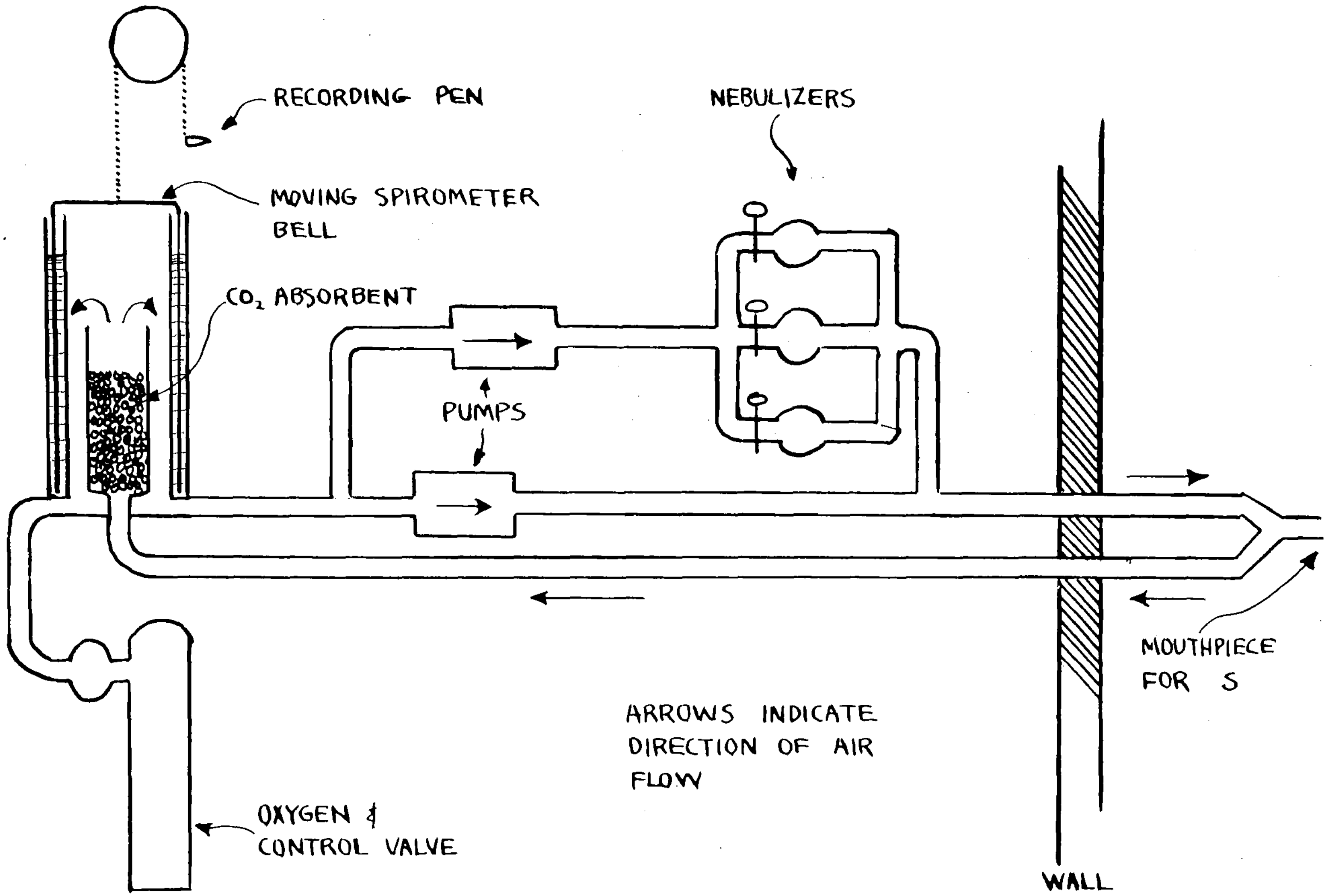


Figure 2

Sloanaker modification of Herxheimer apparatus

The main breathing circuit from the respirometer to S and back was constructed of natural rubber tubing with a 3/4 inch internal diameter which minimized resistance. The side circuit which nebulized the unconditional stimuli was constructed of smaller (1/4" i.d.) tubing to reduce the air volume and elasticity of the system.

The 400 and 1000 cycle tones were generated by a Kronkite pushbutton oscillator, while the CS_{OL} (oscillating light) was produced by a manually operated rheostat which controlled one of the two lights in the S's room. This light was oscillated from zero to 110 volts about forty times per minute.

VI. SELECTION OF SUBJECTS

For the successful induction of experimental asthmatic attacks and proper execution of the experimental procedure, the following criteria were used in the selection of Ss:

1. S must be an asthmatic with severity level of 2, 3, or 4. (Knapp and Nemetz, 1957)*
2. They must be available at least once per week for a period of two or three months.
3. They must be cooperative and be able to give reliable vital capacity measures.

Application of these criteria caused the following loss of Ss. Of a total of 12 Ss the following were lost for the reasons listed.

Subject	Reason lost
Mrs. En.	Due to the unreliability of travel arrangements this S was dropped.
Mr. S.	Recently released from a state hospital, this man was unable to sit still in the apparatus.
Mrs. C.	This S came only one session and gave unreliable vital capacities.
Mr. A.	Poor motivation to come. Discontinued all contact with the experiment and the clinic it was associated with.

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* These levels are defined by the authors as follows:
  - Level 2. Frequent symptoms, well or fairly well controlled by other than steroid medication, taken frequently.
  - Level 3. Frequent, moderately severe, or severe symptoms poorly controlled by medication other than steroids.
  - Level 4. Severe, incapacitating symptoms, unrelieved by medication, except for steroids and/or hospitalization.

Miss W.	Asthma too mild and out of season. Could not induce attacks with mecholyl.
Mrs. R.	Became angry with E and clinic because we would not help her with a housing problem. Came sporadically, three times.

The principal sources of Ss were two in number. Some were or had been coming to the Psychosomatic Research Unit* as patients in psychotherapy. Others were receiving routine medical management of their asthma at the hospital outpatient department.

At the outset it did not appear possible that the Ss could be paid for their participation in this work. Whatever their original motivation for starting, it became apparent that the relationship with E became an important factor in their continuing to come. Because of the non-directive nature of the interview at the conclusion of each session, Ss would often utilize it in a semi-therapeutic way, telling of various difficulties of his present life situation in spite of E's efforts to steer the content solely to the Ss feelings and sensations during the session itself. Finally it became possible to reimburse Ss their expenses incurred in coming to the sessions. This did not appear to be an important motivational factor, however.

* Massachusetts Memorial Hospital, Boston.

VII. EXPERIMENTAL PROCEDURE

Instructions to patient. Patients were contacted by E or by their own therapist and asked if they would be interested in participating in a study about asthma. After a patient so agreed, he was introduced to the apparatus and given an informal paraphrase of the following instructions:

> You have been asked to be a subject in a breathing and heartrate study. The job is a simple one requiring that you sit quietly in a chair for about half an hour while various measures are taken, much like having your temperature and pulse taken.
>
> Here is the place you can sit. You will have this noseclip on your nose. You will breathe through this tube here, and these contacts will record your pulse. It is impossible to get a shock from these. They lead merely to a recording machine in the next room.
>
> From time to time it will be helpful for you to give your vital capacity. That is, whenever this light goes on, take in all the air you can and then exhale all of it. Try doing it now. There is no rush to do it the instant the light goes on. Accuracy in giving a good vital capacity is most important.
>
> You may feel somewhat uncomfortable from time to time, but please try to finish the test and we will be sure that no harmful effects result.
>
> Your participation is very much appreciated. It's only through people like you that we can gain knowledge that will benefit others.

Procedure for conditioning sessions. E placed S in the equipment and entered the apparatus room. As soon as the circulating pumps were turned on, E told S to place the breathing tube in his mouth. Barring any unusual developments, this was the last verbal communication between S and

E for the remainder of the run. S commenced normal breathing in the tube and awaited the turning on of the lamp which signaled him to give a vital capacity. The ideal schedule was as follows.

TABLE 1

Procedure for conditioning sessions

Event	Time between events
1. Take three vital capacities to determine day's baseline.	
	2 minutes
2. Turn on CS to be associated with onset of asthma. (CS_{1000} or CS_{01})	
	1 second
3. Introduce mecholyl into breathing circuit for about 20 seconds.	
	about 1 minute
4. First signs of asthma appear.	
	10--15 seconds
5. Terminate CS, and allow asthma to produce about 30% drop in the vital capacity. Then begin next conditioning procedure to end asthma.	
6. Turn on CS_{400}.	
	1 second
7. Introduce isuprel into breathing circuit for about 20 seconds	
	about 30 seconds
8. First signs of asthma relief appear.	
	10--15 seconds
9. Terminate CS_{400}.	
	about 6 minutes
10. Remove S from apparatus	

The total time required for an experimental run was about fifteen minutes. Once the S was removed from the apparatus, E interviewed him for about ten minutes. S was asked how he felt during the run, whether any vital capacities felt particularly large or small, whether he noticed any wheezing, and what sensations or ideas he had had. Questions were left open-ended to collect material relevant to the S's conception of the experiment, attitudes, and current life stresses.

There was one variation of the above procedure that was necessitated when the S arrived with a considerable degree of asthma already present. This was to omit the induction of further asthma and attempt to condition only asthma termination. This was accomplished by simply omitting steps 2 through 5.

Procedure for extinction sessions. After three or four conditioning trials, an extinction trial was given in order to measure any effect of the conditional stimuli. The procedure, listed below in table 2, is essentially like that of the conditioning session except that the unconditioned stimuli are omitted.

TABLE 2

Procedure for extinction sessions

Event	Time between events
1. Take three vital capacities to determine day's baseline.	
	2 minutes
2. Turn on CS associated with onset of asthma (CS_{1000} or CS_{01}) for 2 or 3 minutes.	
	up to 7 or 8 minutes
3. Watch for any signs of asthma.	
4. Regardless of above results turn on CS_{400} for 2 or 3 minutes.	
	up to 7 or 8 minutes
5. Watch for any signs of asthma relief.	
6. Remove S from apparatus.	

VIII. RESULTS

This section is divided into the following parts:

(1) Findings concerning the importance of the dependent variables.

(2) The similarity of mecholyl-induced asthma and clinical asthma.

(3) Presentation of two cases showing evidence for conditioning.

(4) Presentation of two cases not showing evidence for conditioning.

(5) Presentation of two cases which could not be evaluated.

(1) Findings concerning the importance of some of the dependent variables. Of all the variables measured, vital capacity and the amount of air forceably expired in the first second of the vital capacity (f.e.v. 1)* proved to be the most satisfactory. This was due to the ease of measurement (compared, for example, with respiratory rate, wheezing, and air trapping) and their observed sensitivity. During the induction of mecholyl-asthma, changes in vital capacity and f.e.v. 1 were reliably the earliest variables to change. During mild asthma these were the only variables to show a change consistent with the course of the attack.

The amount of air forceably expired in the second and third seconds (f.e.v. 2, and f.e.v. 3, respectively) was

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* This abbreviates "forced expiratory volume during the first second of the vital capacity." See Fig. 1, for illustration.

often a misleading indicator of asthma severity for the following reasons. Normally, a person can expire most of his vital capacity in two seconds. In asthma, however, this same person's air passages are constricted, impeding the flow of air and leaving <u>more</u> air to be expired during the third second of the vital capacity. Thus, in severe asthma, an <u>increase</u> was often observed in f.e.v. 3. The effect of asthma on the amount of air expired during the second second of the vital capacity was less predictable, with the changes being either toward an increase or decrease in the volume, and sometimes with little change being observed. This is in contrast with the opinions of some clinicians who feel that f.e.v. 2 and f.e.v. 3 are important indicators of asthma. The observed sensitivity of f.e.v. 1 to the asthmatic state supports the report of Gaensler (1951).

In this research progressive air trapping was not a measure of asthma severity because of the difficulty in its quantification. Also, it did not appear in mild asthma, but did sometimes serve as an early indicator of moderately severe asthma during the experimental runs.

Wheezing proved to be a very insensitive indicator of asthma, occurring, if at all, only after large reductions had already occurred in the vital capacity and flow rates.

For the above reasons, vital capacity and f.e.v. 1 are the variables used to measure the conditioning effects.

(2) <u>The similarity of mecholyl-induced asthma and "natural" asthma</u>. The question must be asked concerning the similarity of effects brought about by mecholyl and the conditions observed in clinical asthma. Given in adequate dosage, the inhalation of vaporized acetyl-beta-methacholine chloride produced the following changes in the asthmatic Ss:*

a. marked reduction of the vital capacity,

b. marked reduction of f.e.v. 1,

c. an increase in the air trapped in the lungs,

d. an increase in wheezing,

e. the sensation of tightness and labored breathing.

All of the above results are routinely observed in natural "intrinsic" asthma, and can be understood as resulting from the primary mechanical lesion in asthma--bronchoconstriction. Mechanically, then, mecholyl-asthma and natural asthma appear to be highly similar.

Chemically an equivalence cannot be positively stated. Little is known about the chemistry of asthma and there is not sufficient room to discuss this matter here. It is assumed that mecholyl, a parasympatheticomimetic drug, stimulates the smooth muscle in a way similar to the acetylcholine normally released by the sympathetic nerves, producing contraction of the muscle. It was found that the

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* Administration of this same concentration of mecholyl in large doses (inhalation up to two minutes) produced no bronchospasm in any of four normals or one asthmatic whose asthma was out of season.

severity and speed of onset of mecholyl-asthma was a function of the mecholyl dosage. Inhaled mecholyl does not seem to serve simply as a "trigger" of some asthmatic process. Because the experimental design required terminating the induced asthma with Isuprel, the degree to which a S could recover from mecholyl-asthma could not be observed. Such an experiment would be necessary to determine if the continued presence of mecholyl is necessary to maintain an asthmatic attack.

Drugs are used to protect persons against clinical asthma. One of them, inhaled Isuprel, reversed both mecholyl-asthma and natural asthma indicating their similarity in responsiveness to Isuprel. A second drug, cortisone, which seems to relieve clinical asthma did not seem to provide measureable protection against the induction of mecholyl-asthma. This parallels the finding (p. 26) that neither ACTH nor cortisone lessened histamine-or antigen-induced asthma in the guinea pig.

Another similarity of mecholyl and clinical asthma was the sensation of oncoming asthma. In general, reductions in the vital capacity up to 35% produced no sensations in our seated Ss. (Had they been physically active it is possible that they might have been aware of their reduced ventillatory capacity). As greater reductions were produced the sensations of mecholyl-asthma reported by the S were the same as for their regular asthma. These sensations, interestingly enough, were specific for the individual and included feelings of "heavy air", "tightening in the chest", "shortness of breath", and "feeling shaky." The sensations of mecholyl-asthma were for each S the same as those of his natural asthma.

Although it does not permit comparison with clinical asthma, it was observed that the presence of what the S described as a common cold often made the induction of mecholyl-asthma more difficult. It is possible that this could have resulted from the protective effect of extra mucous in the bronchae.

(3) Two cases showing evidence for conditioning. Of the four Ss with sufficient data to analyze, two, Mrs. S and Mr. M show evidence for conditioning. Both of these cases are described below. The basic conditioning data is contained in appendix 1.

Mrs. S.

> Essential findings: This S shows evidence which suggests that after experiencing marked mecholyl-asthma in the experimental situation she has a tendency to experience a sudden paroxysm of asthma when again in the situation.

Mrs. S was a middle-aged housewife who has had asthma since the age of two. Overtly cooperative and intelligent, she was a regular attender of the conditioning sessions. She entered the experiment before the proper dosages of mecholyl had been worked out, and for some time was given an insufficient dosage resulting in very few conditioning trials with the onset of asthma. Conversely, she often arrived with some degree of asthma and was able to have her asthma relieved in the conditioning sessions. In all, she had six conditioning trials with the onset of asthma (i.e. pairing it with CS_{01}) and eighteen conditioning trials with the termination of asthma (pairing Isuprel and CS_{400}). She had a total of ten extinction (test) trials with the above stimuli. None of these extinction trials showed any change in her asthma.

There is evidence, however, that she did become conditioned to the experimental room and surroundings. This is now described in detail.

For several trials prior to the 5th of December, Mrs. S. had, in accordance with the experimental procedure, received a dose of mecholyl for the induction of asthma, and this had each time been paired with CS_{1000}. However, as mentioned above, the dose of mecholyl was insufficient to produce an asthmatic response. Since repeated presentations of the conditioning stimulus without successful production of the UCR (asthma) was not desirable, it was decided to stop presenting a conditioning stimulus and to give gradually increasing test doses of mecholyl in order to find the proper concentration.

On 5 Dec., the experimental concentration of mecholyl had again been increased and since no effect was yet expected, no CS_{1000} was presented to the S. This resulted in an unplanned and significant event. For the first time an adequate dosage was given and a 73% drop in the vital capacity was produced. This was the most severe attack produced in the course of the entire experiment. Although not dangerous, it produced dramatic conscious asthma in which Mrs. S. had to labor for each breath. This attack was then relieved by a CS_{400} conditioning trial. S's belief that E would not let anything happen to her encouraged her to remain in the apparatus. The following several trials seemed to indicate that this trial, given without any CS for the onset of the attack may have caused conditioning to the room and/or experimental session.

First drawing attention to this possibility were the events which came three sessions later on 15 Dec. On entering the experimental room, she proceeded with the customary card-sort test of emotion prior to being placed in the apparatus. As soon as she began the card-sort test she noticed a developing tension and tightness in her chest which surprized her because it came on so quickly. It was a sensation that had definitely not been present in the waiting room a few moments before. She could not understand it because (as she said in the taperecorded interview), "I don't know, I certainly haven't experienced um, any, um, anything unpleasant in terms of coming here that would have caused that kind of emotional reaction to the test or anything."

Why had this "conditioned asthma" reaction not occurred in the two sessions between the conditioning trial on the 5th and the appearance of asthma on the 15th of December? The best explanation is her use of drugs. Just prior to each of the two intervening conditioning sessions when the response did not appear, S used her Isuprel nebulizer within one half hour before entering the experimental room. Thus it is possible to have obtained a protective effect and prevented the appearance of the CR. The fact of her use of the Isuprel is itself interesting since these were the only times she used the medication just prior to an experimental session. The day of the appearance of the "CR" she had not used Isuprel for an hour and a half.

Circumstantial evidence that this sensation of asthma onset on 15 Dec. was related to an actual asthmatic change is the fact that her vital capacity and f.e.v. 1", measured immediately after entering the apparatus, were the lowest values of any of her sessions. Although no measures were available before she entered the experimental room, there is good evidence that her breathing was not so severely impaired since she had experienced no difficulty climbing the two flights of stairs to the waiting room. Her first vital capacity in the apparatus showed a reduction of 66% below her symptom-free level, and such a degree of constriction, if present when climbing the stairs should have caused marked difficulty.

If this was a CR that occurred on 15 Dec., what became of it? The next session was 19 Dec. At that time S had taken Isuprel ten minutes prior to the experimental session and again no sensations were reported. When she entered the apparatus, however, her v.c. and f.e.v. 1" were again at an extremely low level and S felt her breathing was a bit more difficult.

By 21 Dec., the next trial, S had been taking cortisone for three days and her asthma had begun to abate. Nevertheless she reported slight increased tightness on entering the apparatus. Her vital capacity was 46% below her symptom-free level.

The experimental sessions were then interrupted by a three week Christmas period. When Mrs. S returned after this period, this "conditioned" phenomenon did not reappear.

Summarizing briefly, there seems to be evidence for the temporary appearance of conditioned asthma. In this case the conditioned stimuli were those present the first time mecholyl-asthma was produced--the room and experimental situation.

What did Mrs. S think about her asthma attacks and the experimental procedure? It has been said that human Ss, uninstructed, will tend to become self instructed. In this case the process was quite evident. Not satisfied with the vague standard explanation of the purpose of the experiment, Mrs. S. revealed the following hypotheses in her post-run interviews.

Table 3

List of hypotheses related by Mrs. S. in post-run interviews

Date	Statement
2 Nov. 1960	What are the sounds? There are two. Felt they were planned. Some sounds might make breathing more difficult. For example, a baby's crying.
14 Nov.	Did E give her Isuprel? S suddenly felt better when the second sound went on.
16 Nov.	Second tone was accompanied by easier breathing. Is E doing a Pavlov?
28 Nov.	Feels no change in breathing. Doesn't mention tones.
29 Nov.	Tones are irritating. After they're on a while you don't notice them any longer. It's a relief when they're turned off. Do tones affect breathing?

TABLE 3 Continued

Date	Statement
5 Dec.	(Large attack of asthma without any CS.) No mention of tones. Talks about asthma and the unusual swiftness of the attack.
7 Dec.	E must be giving her something to produce and relieve asthma. The second time the lights flickered S felt tightness. After the tone it was relieved. Had Isuprel sensation. Expected to have asthma produced this time.
14 Dec.	Breathing easier about the time of the tone.
21 Dec.	Flicked the light and made her wheeze. Relieved it and played the tone. The only thing missed was the two tones. Felt nothing the first time the lights flickered.

In this series of statements it is clear that S develops her own particular awareness of the experimental procedure and makes various confirmations and rejections of her hypotheses. In the first few trials in which CS_{1000} was given without reinforcement she learned that not all environmental changes were accompanied by internal changes. She described how she adapted to the tones and didn't realize they were on. Then comes a puzzling attack not accompanied by any changes in the environment.

In the course of the interviews, when E failed to confirm or deny any of her hypotheses, Mrs. S. came to expect something devious. After the 5th of December attack S stated that she expected something to happen during the sessions.

This S, who was the only one reporting the presence of two tones and who had the idea of conditioning and the association of physical changes with the tones, did not show conditioning to the tones. This is further discussed in the final section of this paper.

Mr. M.

> Essential findings: this S shows evidence for conditioning occurring to both the experimental situation and to the presented conditioned stimuli.

Mr. M. was a 34-year-old single musician who first had asthma in his early twenties. He had been in psychotherapy for some time at the clinic and was described by his therapist as preoccupied with bodily processes, guilty over strong dependent wishes, and a generally obsessive-compulsive character with paranoid features. Mr. M. was a regular attender of the experimental sessions, but not without a great deal of obvious conflict. He tended to make the post-run interview sessions into therapeutic sessions in which he expressed both resentment over coming, and fear that the experimenter would abandon him as everyone else had.

First, let us examine the conditioning data with the light (CS_{o1}) and the tone (CS_{400}). Mr. M. had a total of seven conditioning trials pairing CS_{01} with the onset of asthma, and a total of 21 conditioning trials pairing CS_{400} with the termination of asthma. There were seven extinction (test) trials with the CS_{400} and five extinction (test) trials with CS_{01}. The combined results of reactions to these stimuli are present in fig. 3. In accordance with the standard experimental procedure, each extinction trial consisted of three vital capacities after the presentation of the conditioned stimulus. It was therefore possible to average together over the seven extinction trials to CS_{400} the first vital capacity in each extinction trial, and to do the same with the second and third vital capacities across the seven trials, obtaining a curve showing the average (mean) reaction to CS_{400}. The same was done with the five extinction trials to CS_{01}.

Following the five unreinforced (test) presentations of CS_{01}, the vital capacity is seen to decrease as one would expect if conditioning had taken place. Following CS_{400}, the vital capacity is seen to increase. These curves show a change which is not only in the proper direction but is progressive over time as one would expect if it reflected a change in the state of the lungs. The curves indicate a change about one fifth to one tenth of that produced in the conditioning trials. This supports a conditioning hypothesis since the CR is usually of lesser magnitude than the UCR. Evidence for conditioning to the CS can be only probable,

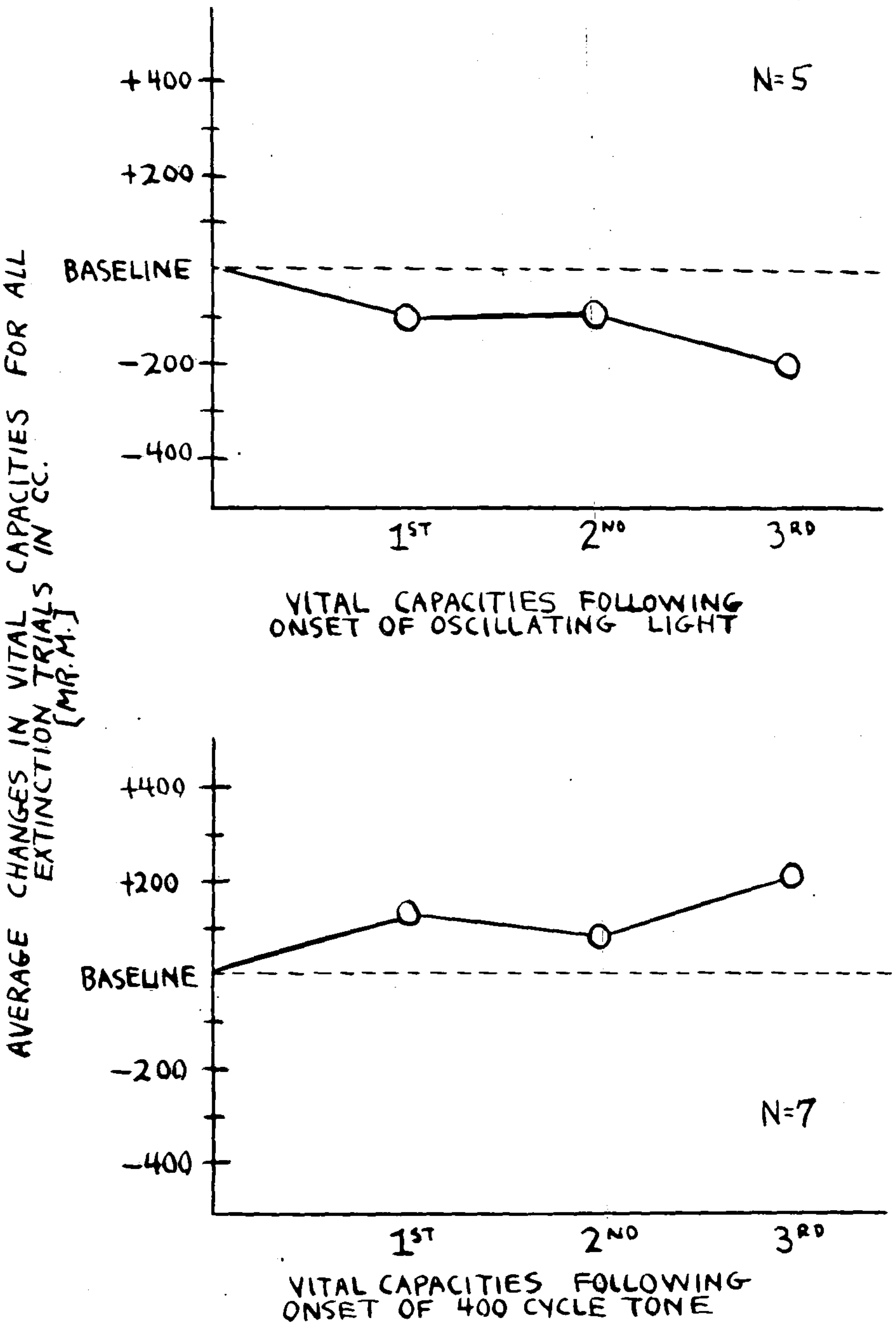

Figure 3

Average effect of the conditioned stimuli for Mr. M. (see text)
Upper figure: baseline is average of the three preceding vital capacities.
Lower figure: baseline is the vital capacity preceding stimulation, i.e. the 3rd vital capacity in the upper figure.

however, because the changes--about 200 cc in five minutes or about 7% of the baseline value--do not exceed the 10% change specified in the original criteria. The reliability of the reaction and the progressive nature of the change do lend the change credibility. It is also possible that the observed changes might have been greater had more vital capacities been taken, and a greater time allowed for the reaction to continue. Unfortunately, E was not aware of these trends until detailed data analysis was done following the experiment.

As already described in relation to figure 3, five individual extinction trials were averaged to show the mean response to CS_{o1}. Examination of these individual extinction trials to CS_{o1} reveals an interesting feature. All extinction trials are in the expected direction, i.e. they show a decrease in the vital capacity, except the first which shows a progressively <u>increasing</u> vital capacity in response to CS_{o1}. The interesting feature is that there are no conditioning trials between that unsuccessful first trial and the next three trials which were highly successful. The major intervening event between this first extinction trial and the next three extinction trials which were massed (consecutive) was a 2½ week Christmas period during which Mr. M. was not involved in the experiment. There is not sufficient data to understand what may have been involved in the changed action of CS_{o1}. It was during this same period that the response to CS_{400} changed, the response changing from uncertain to strongly positive.

In summarizing the individual extinction runs it can be said that the largest changes and the best differentiation between the action of CS_{o1} and CS_{400} occurred after this 2½ week cessation of the experiments.

There is evidence in Mr. M's data for conditioning also occurring to the experimental situation. The principal evidence lies in the trends seen in his first three vital capacities in each experimental session. These three vital capacities were used to determine his baseline for each day and were always taken prior to any experimental manipulation. A directional trend, i.e. a progressive change in one direction for all three vital capacities was sometimes observed. In the case of Mr. M. these assumed a rather distinctive pattern. This is shown in table 4.

TABLE 4

Frequency of trends in Mr. M's first three vital capacities in each session

Blocks of trials.	Conditioning being done.	Frequency of trends.
Sessions 1-9	S experienced only asthma relief.	up: 6 down: 0 no trend: 3
Sessions 9-17	S experienced asthma and asthma relief.	up: 0 down: 0 no trend: 8
Sessions 17-25	S experienced 2 attacks, 6 reliefs.	up: 5 down: 2 no trend: 1

For the first block of nine trials, S experienced only Isuprel-induced relief of asthma in the apparatus and showed this preponderance of upward trends in his vital capacity at the beginning of the sessions. The next block of 8 trials in which asthma was both produced and relieved, the trends disappeared completely. In the final block of 8 trials, there were 2 provocations and 6 reliefs, and the trend pattern parallels this, containing a majority of upward trends. All these patterns differ markedly from a random pattern* which would have the form of:

* A trend is defined as a consistent change in one direction in the three vital capacities used to determine the baseline at the beginning of an experimental session. The first three vital capacities can be ranked in order of their magnitude. Of the six permutations of the ranks 1, 2, 3 only two are trends, one up, the other down.

up: 1
down: 1
no trend: 4

What did Mr. M. think about his asthma attacks and the experimental procedure? Mr. M., like several Ss, commented on the occurrence of the tones and light when interviewed following a trial. Comments such as, "Oh, yes, I heard that 'ping' again," or, "the lights flickered a bit" were made. He did not, however, consciously connect these changes with other sensed events such as seeming to feel a bit of tightness, or thinking at one point he tasted "something like Isuprel." He did occasionally report feeling his heart pounding after CS_{400}, however.

When asked if he could pinpoint the time during a run when he "felt better", he would refer to the "end of the run", "somewhere in the middle", "after the ping", etc. More often than not he incorrectly identified the time.

This S's paranoid suspiciousness and obsessiveness made him particularly sensitive to the possibility that a chemical was being put in the breathing apparatus, but at the same time his overelaboration of all sorts of hypotheses about his asthma served to mask the real relationships between the conditional stimuli and bodily change.

(4) Two cases not showing evidence for conditioning. Of four Ss with sufficient data to analyze, the remaining two, Mr. B. and Mr. D., do not show evidence for conditioning.

Mr. B. had a total of 20 conditioning trials with the termination of asthma, and 17 with the onset. CS_{1000} and CS_{400} were the two conditioning stimuli used. Extinction trials in both cases show no change in the vital capacity.

In spite of the many lung changes produced in the course of the conditioning trials, this S, an 18-year-old negro boy, seemed unaware of the true nature of the experiment. When questioned, he could name particular vital capacities as feeling good or bad, but the correspondence between his report and the facts was poor. He did, however, observe other bodily effects of Isuprel, the sensations for him being those of heart acceleration and feeling hot on the skin. He never verbally connected this experience with the 400 cycle tone, but described it as coming "near the end", or, "the second vital capacity from the end".

Just as Mr. B. was insensitive to the number and nature of the tones and the changes in his respiration, he was insensitive to his emotional state as measured by a card-sort test of emotion.* Although constantly urged to sort more emotion statements into the "yes" piles (meaning the emotion was present), he never used more than three or four such statements. This is extremely unusual and is the most

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* Unpublished test designed by the writer and Dr. P. H. Knapp. It is an IBM-scored card sort test of current emotion yielding independent scores in 12 categories of emotions.

constricted sorting pattern seen in administering this test to more than 70 subjects.

There seemed, in this S, to be some interaction between obviously low verbal fluency making it difficult for him to report internal change, and some tendency to deny the more threatening aspects of the situation. There is ample evidence in the interviews for the extensive use of denial. One example was an incident in which he was explaining the necessity of changing an appointment. In the course of the interview he offhandedly remarked that his house had burned down the night before.

That the relationship to the E was important, however, was shown in the changed nature of asthma outside the experimental situation. Previous to becoming a S in the experiment, Mr. B. had been hospitalized with severe asthma 8 out of 11 weekends. In the course of the experiments, he was hospitalized once in two months.

Mr. D. had a total of 12 conditioning trials with the termination of asthma and 8 with the onset of asthma. CS_{1000} and CS_{400} were the conditioning stimuli used. Extinction trials in both cases show no change in the vital capacity. Although there is some indication that CS_{400} may have had some positive effect, there are not enough extinction trials to ascertain this.

Mr. D's attitude toward the experiment was brusque and businesslike. Always punctual, he was cooperative and exacting in his interview reports. Asked after the completion of the experiment if he noticed any sounds, i.e. the CS he said he had heard some "pinging" sounds but had paid no attention to them figuring they were part of the machinery. He said he was used to working in a noisy office and could ignore such sounds easily. He could not recall how many different sounds there had been or their relationship to any other events.

In the early trials, however, Mr. D., like all other Ss, had turned toward the source of the sound indicating that it originally was perceived, producing an orienting reaction.

(5) Two cases which could not be evaluated. Although no data will be presented for the two remaining Ss, they will be reviewed since they were carried through a substantial part of the experiment. They are Mrs. E. and Mrs. G. The latter had seven successful conditioning sessions, but lived so far away that she was able to get in for only two extinction trials neither of which showed any evidence of conditioning to the stimuli or the situation.

Mrs. E. had two successful conditioning trials with the onset of asthma, and two with its termination. She presented a problem that was not at first recognized--her vital capacities were not reliable. This gave the impression that she did not react much to Isuprel, and also led the author to the erroneous conclusion that the original concentration of mecholyl (1:40,000) was correct when S showed a 500cc drop in vital capacity in reaction to it. Her unreliability became obvious, however, in both her attitude and extinction trials. In the experimental situation she several times fell asleep, experienced hot flashes, pains, felt faint, etc. The nature of the changes observed in her vital capacity in an extinction trial of CS_{01} were: -725, -550, -100, -625, and unlike any of the other S's results, these showed little correlation with the f.e.v. 1". Her results also differed in that they appeared to be random changes, and not progressive as required by the criteria of the experiment. Final confirmation came when it was demonstrated that S could, with reinstruction, give much bigger vital capacities than she had been giving. It was then concluded that her data was too unreliable to interpret.

IX. DISCUSSION AND CONCLUSIONS

This section is organized as follows:

(1) Methodological contributions
(2) Properties and measurement of mecholyl-asthma
(3) Discussion of conditioning results
(4) The nature of conditioning

(1) Methodological contributions.

(a) Equipment was developed which, in addition to permitting the necessary experimental operations while concealing them from the S, measured the dependent variables of vital capacity and f.e.v. 1.

(b) Concentrations of an aerosol of acetyl beta-methacholine chloride were found which would reliably produce a desired degree of bronchoconstriction in asthmatics.

(2) Properties and measurement of mecholyl-asthma

(a) As observed in this work, mecholyl-induced asthma appeared the equivalent of clinical asthma in its effects on the mechanics and dynamics of respiration, and in its reversibility by the inhalation of Isuprel.

Sensitivity to the concentrations of mecholyl used in the experiment, not found in normals, was apparently lost in seasonal asthma during the out-of-season phase.

(b) A sufficient and regular change in the dependent variables constituted the operational definition of asthma. Operationally the experiment attempted conditioning of these variables from which bronchoconstriction, the primary lesion in asthma, could be inferred. Although motivational factors could alter the S's effort and cooperation thereby affecting these dependent variables, Ss who showed erratic results were eliminated from the experiment.

In general, changes in the dependent variables were thought to reflect a mechanical change in the properties of the lung if, after experimental manipulation, changes observed were progressive curves, and if, in the absence of experimental manipulations, nothing but small random variations appeared.

(c) In the measurement of functions controlled by the autonomic nervous system, certain problems ensue which are described in the "law of initial values". These problems arise because the level of the variable being investigated is the resultant of two usually opposing systems--the sympathetic and parasympathetic.

The problem is succinctly stated by Wilder (1950).

> The response to agents stimulating the function under investigation depends to a very large extent on the initial level of that function. If that level is low there is a tendency to marked increase; if that value is average this tendency is less marked; if the initial value is high we shall often find minimal or no increase and quite often a paradoxical drop in the examined function. The exact opposite is true for inhibitory agents.

Vital capacity is an autonomic resultant and as such would be expected to follow this law. However, the asthmatic state represents a disturbed homeostatic balance and may be seen as the result of a disordered system. In this disordered system the law of initial values may not hold since in persons with low vital capacities it was relatively easy to produce a further increase in asthma, while persons who were in better health--in whom the vital capacity was large--it was found more difficult to produce an increase. That the law of initial values may have to be altered in describing disordered systems can be only suggested here since a higher vital capacity was often due to the effects of drugs which might reduce the action of mecholyl.

(d) In observing clinical asthma, Knapp and Nemetz (1960) distinguish frequently occuring prodromal emotional states--excitement and arousal, or depression. These authors raised the question of whether these emotional states might be a reaction to the dimly-perceived developing asthma. They concluded this is not the case since the strength of the emotions seemed too great in proportion to the danger or threat of asthma.

The results with mecholyl-induced asthma support this position. It became apparent that considerable asthma could be present without a person's awareness and without any strong emotional reactions. Reduction of the vital capacity by 35 to 40% of normal elicited comments that, "The run was as usual." "All vital capacities felt the same." "Routine."

It would therefore be difficult to understand the prodromal emotions only as a response to already developing asthma.

(3) Conditioning results

(a) Discussion of successful cases.

In the case of Mrs. S. conditioning was observed to the situation but not to the tone or light. Unlike the other Ss, Mrs. S. was aware that her breathing changed during and after the presented conditioned stimuli. Although the switch from CS_{1000} to $CS_{\odot 1}$ confused her hypotheses about the nature of the experiment, she consciously expected something to happen. She was constantly trying to conceptualize her experience and to understand what E was doing. Expecting E to change her breathing after the CS, Mrs. S. was vigilant and prepared for the expected change. She asked E if he was trying to "Pavlovize" her. There are no other indications of the nature of such vigilance, but it would seem to inhibit the formation of conditioned reflexes.

The successful conditioning trial was quite different. A connection is apparently formed when S is caught "off guard." Suddenly, without warning, severe asthma is produced. In addition the UCR is of large magnitude and provoked considerable anxiety though S felt reassured that E would not let anything bad happen to her.

That the possibility the act of expecting an association between asthma and the light might have prevented the formation or expression of a connection would seem related to the common experience of steeling oneself for something unpleasant. Unexpected or intense stimuli are threatening to an organism and can, depending on their intensity and the condition of the organism, evoke startle reflexes, avoidance behavior, traumatic neuroses, or fainting. Perhaps they also facilitate conditioning. It is necessary that an organism protect itself against such stimulation. Another method for defending against such stimulation can be seen in the obsessive mechanism of overplanning and scheduling to avoid the unexpected or of understanding something in order to reduce its danger. This S showed all these behaviors in relation to the presented conditioned stimuli.

With the addition to the above the hypothesis that these types of defensive operations are impaired by fatigue or prolonged stress, this forms an interesting parallel to the writing of Michlova (1960) using the theory of the "dominant." She states that a dominant point of excitation (in Pavlov's sense) in the cortex, showing itself as a strong CR, is best achieved when the nerve impulses aroused by the stimuli are not inhibited and can "penetrate the cortex," this being most apt to happen in conditions of stress or fatigue.

One interesting additional feature of this case is that when the conditioned attack came, S did not connect it with her previous experience in the room! She even denied that she had previously experienced anything unpleasant in the room (with a clinically significant pause before the word "unpleasant). This is reminiscent of some findings of experiments creating microneuroses.

Mr. M., the second S to show probable conditioning, shows change in response both to the situation, and CS_{01} and CS_{400}. Evidence, again, is only probable since the changes produced in the vital capacity are not large. The magnitude of the UCR was considerably less than in the previous case, and there was little if any affect or awareness connected with it. (The role of low affect is discussed in a later section.) In connection with the above discussion on stress and conditioning, it is the writer's estimation that Mr. M. was the most heavily stressed of the experimental Ss. Not only had he to cope with the intense personal conflicts already described, but just prior to the successful extinction trials, his aunt, to whom he was very close, was on the danger list of a nearby hospital. Under the hypothesis that stress should facilitate conditioning, conditioning should have been likely in this individual.

This S had one thing in common with Mrs. S. which may also have increased the emotionality and involvement in the situation. Both were psychiatric outpatients in the same clinic where the research was being done, and had been asked by their therapists to participate in the experiment.

(b) Discussion of unsuccessful cases.

Why did conditioning not appear in Mr. B. and Mr. D? Razran (1958) feels that low and medium attensity (attention value) of the conditioning stimuli contribute to the most effective conditioning. In this experiment no instructions had been given for the Ss to attend to the conditioning stimuli. The attensity value of the stimuli for Mr. B. and Mr. D. was considerably lower than for the two previous Ss, in fact they could not recall how many different kinds of stimuli there had been. The lack of differentiation between the stimuli associated with the onset and with the termination of asthma was facilitated in these two cases by using two tones (CS_{1000} and CS_{400}) instead of CS_{o1} and CS_{400} as with the two successful cases.

A second important feature in human conditioning according to Razran is the affectivity of the response. There is little doubt that if all four Ss were ranked on general affect arousal during the conditioning work that the two failures would score the lowest. This factor of emotionality-affectivity was mentioned by Razran in relation to the UCR specifically, although it has been mentioned that generally anxious Ss condition most readily. This observation on general affect arousal concurs with Dekker, Pelser and Groen (p. 29) who felt that the loss of conditionability in one of their asthma patients was related to becoming less emotional and dependent on the doctors following group therapy.

(4) The nature of conditioning.

(a) This research does raise some questions about the nature of the conditioning process itself. Conditioning as done in this research differs in an interesting way from much of classical conditioning. Note particularly the action of the UCS, acetyl-beta methylcholine chloride, which mimics the action of acetylcholine normally released by parasympathetic fibers. It acts directly on the smooth muscle of the lung, producing contraction (Hoff and Breckenridge, 1951). This, then, does not necessarily stimulate a sensory-motor arc! The significance of this is seen on examining Pavlov's original schematic diagram of the conditioned reflex (fig. 5).

It is seen here that there must be a representation

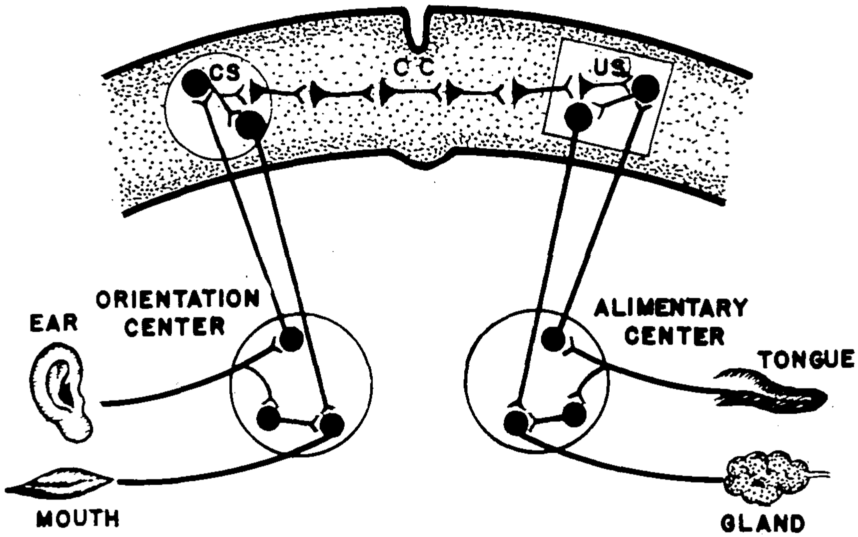

FIGURE 1. Scheme of the conditioned reflex arc. Key: CS, conditioned stimulus; US unconditioned stimulus; CC, conditioned connection.

Figure 4

Taken from Asratyan (1961)

of the unconditioned reflex in the nervous system for an association to occur. Although more complex models for conditioning now exist (Anokhin 1961) this same requirement remains.

Even if the direct action of mecholyl does not activate a sensory-motor arc, it still remains a possibility that the fact of muscle contraction would activate sensory fibers. Since in the normal individual the author's doses of mecholyl produced no change in the vital capacity or f.e.v. 1", the possibility exists that a reflex involving sympathetic activation countered the contractive effects of the mecholyl in normals. This is in the area of speculation, however, since in the normal, mecholyl may simply be destroyed chemically by the action of cholinesterase, or other mechanism.

(b) From what has been observed, would it be correct to consider conditioned asthma merely as a S-R connection? Can an exteroceptive stimulus come to directly change the state of the lungs by connecting a sensory input with a parasympathetic discharge? Although this model may be adequate to describe conditioning in some lower organisms or human infants, it does not do justice to the complex events observed. In this section, the sign-significate theory of learning will be discussed as a model. In this theory the CS (sign) induces an expectation-set that the UCS-UCR is to follow. What happens after the presentation of the CS is seen as a preparation on the part of the organism for what it expects will follow.

Mowrer (1960) in his revision of two-factor learning theory presents data on the importance of inferred emotional states and expectation. "In two-factor theory expectations are of two major varieties: hopes and fears, representing, respectively, anticipation of good and bad events to come." (p. 325) He sees the stimulus relationships (CS before UCS) used in classical conditioning as being the way these anticipations develop. Further, these expectations have an emotional component, i.e., they must involve the autonomic nervous system, the behavior of the internal organs, and the general biochemistry of the body. One important point here is that what gets conditioned is not a simple reflex, but an expectation (a central, more complex event?).

This is very important for the understanding of the literature on the conditioning of respiration. That events transpiring between the onset of the CS and the appearance of the UCS-UCR may be viewed as preparatory for that which is expected to follow can be seen in the following experiment by Warner who was attempting to condition the behavior of rats to shock.

> To the shock (UCS) they would hop frantically about and breathe rapidly; to the CS (bell) they would hold their breath and wait tensely. (Warner 1932, p. 134)

The inferred state of expectancy also turns out to be very relevant to the conditioning of guinea pig asthma. The conclusion has been offered in a previous section that the respiratory change observed in "conditioned guinea pig asthma" could not have been true asthma. This conclusion was deduced from the fact that the respiratory change was observed <u>immediately</u> after the presentation of the CS, and this did not resemble the gradual changes one would expect if an underlying autonomic change was taking place in the lung. This conclusion has just been confirmed in a very recent article (Schiavi, Stein, Sethi, 1961). Their research conclusively demonstrates that the variables of wheezing and gasping previously used as measures of conditioned asthma in animals (Ottenberg et al 1958) were a reaction to a fear-pain stimulus and that no asthmatic bronchospasm was involved*. What was conditioned, then, was a state of emotional expectancy of which breathing irregularity seemed to be a part.

Respiratory change in sheep and goats subject to

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* The authors used the standard method of inducing anaphylactic asthma in the guinea pig and attempted to condition this to the experimental situation as reported in previous experiments. They found the same conditioned gasping and wheezing, but employing a direct measure of asthma (airway resistance, which they could measure in an acute experiment) found no change in the asthma itself. In a second experiment with fresh guinea pigs, they found it possible to produce the same non-asthmatic wheezing and gasping with a strong electric shock instead of anaphylactic asthma as the UCS.

painful or monotonous conditioning procedures has been observed by several investigators including Liddell (1951). This change, consisting of loud raucous breathing and apparent respiratory difficulty has been felt to be asthmatic in nature.

> In these experiments we have a closer approximation than heretofore to an adequate test of French and Alexander's "suppressed cry" theory of bronchial asthma with animal subjects. Our young goats separated from the mother are helpless and lonely in the laboratory room. They can do nothing to keep the lights from going out every two minutes and their bleats do not bring the mother. Finally, bleating is suppressed, movement becomes curtailed and rigid, and, to judge from the sound of the little goat's labored breathing, it is experiencing respiratory difficulty. (Liddell 1951, p. 147)

In light of the above discussion and the recent results of Schiavi, Stein and Sethi it appears that the respiratory changes observed in these animals may in fact be related to a general emotional-expectancy about the conditioning and may be enhanced by the absence of the mother, but that these respiratory changes have little to do with asthma.

The relevance of a connectionist view versus an expectancy view to interoceptive conditioning is important. For example, common dependent variables such as the GSR, heartrate, vasoconstriction and dilation, respiration rate, peristalsis of the intestines, and report of sensations can all be measures of this expectancy-emotion set, rather than conditioned responses i.e. what is achieved is signalization, not simple stimulus substitution. This problem is particularly critical in the conditioning of the internal organs as contrasted with skeletal conditioning because it is well documented that visceral change is an integral part of emotion whereas the eye blink, for example, is not. The critical problem in interoceptive conditioning may be the arousal of a particular emotion-expectancy, the physiological manifestations of which are the "conditioned response."

Reiser (1961), approaching the problem from a somewhat different area of study may be saying the same thing when he states that clinical disorders are concerned with deep (dynamically or neurophysiologically) levels, and that laboratory research is not apt to tap these levels. What he seems to be saying is that laboratory researchers often overlook the problem of emotion-expectancy arousal and/or that adequate arousal is difficult in the setting of the scientific laboratory.

To temper somewhat the emotion-expectancy view of conditioning, however, Osgood (1953) has pointed out that to regard the conditioned response as a preparatory adjustment is largely an evaluative observation by the experimenter and does not describe how the various aspects of this preparatory act are selected.

On the one hand it is not difficult to feel that some of the components of an emotion-expectancy are innately selected. For example the typical components of the body's emergency reaction: elevation of the blood pressure, contraction of the pupils, vasodilation in the musculature, etc. seem to be innately determined. On the other hand it is difficult to see how a response such as bronchoconstriction could become part of an emotion-expectancy set. There would seem to be two major possibilities.

The first is that bronchoconstriction _is_ an integral, innate part of some emotional state. Since there is no data available here, this might be a fruitful area for further research. It would be possible to measure the degree of bronchoconstriction during strong emotion aroused by life situations. In the opinion of some clinicians, for example, strong sexual arousal may be accompanied by constriction of the bronchae.

The second possibility is that there is _no_ emotional state in which bronchoconstriction is _normally_ a part. One must then ask how bronchoconstriction could _become_ an integral part of an emotional state. This involves the whole question of how emotional states are integrated, and the problem might be studied as a problem in intero-interoceptive conditioning. (Here, both the CS and the UCS are internal). This presumably would involve contiguity of asthma (UCS) and an emotional state (CS) so that arousal of the emotional state would elicit further visceral responses conditioned to it. This formulation closely approaches the clinical theory of Deutsch who feels that the coexistence of respiratory disorder and an emotion-conflict situation in infancy is a necessary prerequisite for the development of asthma in later life, and that the asthma is aroused when that emotion-conflict is again aroused. In this case, postulating an internal CS, helps answer the question of what maintains an asthmatic attack once it has started. Although the continued physical presence of a stimulus is not required to maintain a reaction (Pavlov's dogs continued to salivate long after the bell stopped ringing), the arousal of some internal stimulus (in the sense that it must be "aroused" it is a mediating process) which the person then carries with him, helps solve the problem of how an attack can be maintained for days or weeks.

(c) This experiment attempted to condition changes in the mechanical properties of the bronchae to an external stimulus. It has appeared that the expectancy of having asthma or experiencing the relief of asthma is not sufficient to produce that change. This is congruent with the findings of White who treated ten asthma patients with hypnosis and suggested relief of symptoms to them: easier breathing, lessening of tension and bronchospasm, and an increase in confidence. Respiratory variables were measured. "Although most patients reported improvement, hypnosis had no predictable effect upon respiratory function" (White, 1961, p. 278).

The fact that conditioning does not automatically result from the contiguous presentation of asthma and an external stimulus, and the complexity of the conditioning situation which became apparent from the detailed examination of individual cases, has led to discussion concerning the nature of conditioning with special emphasis on the newer area of interoceptive conditioning. This has provided two possible avenues for further exploration.

(d) The application of interoceptive conditioning techniques to psychosomatic problems holds considerable promise. Among its advantages: by allowing experimental manipulation and measurement of the symptom and a degree of environmental-experiential control, it permits the direct study of symptom acquisition and loss.

APPENDIX I

Tables of conditioning and extinction data for individual subjects

The table for each S is divided into three columns. The first shows the data of the experimental session. The second tells what was done with the CS associated with the onset of asthma. The third column tells what was done with CS_{400}, the stimulus associated with the termination of asthma.

Data is entered in the table for all extinction trials. The following is a sample entry.

Date	CS_{o1} trials	CS_{400} trials
x Jan. 61	ext. tr. #1 v.c. -100, -200 f.e.v. -50, -50	

This would mean that on x Jan. 61, the first extinction trial with the oscillating light conditioned stimulus was tried. Two vital capacities were taken. The first was 100cc below the baseline, the second was 200cc below the baseline.

The one second forced expiratory volume given during the first vital capacity was 50cc below baseline, as was the second f.e.v. 1.

TABLE 1

Mrs. S. Conditioning and Extinction Trials

Date	CS_{1000}	CS_{400}
1 Nov. 1960	- - - - - adaptation to apparatus - - - - -	
2 Nov.	CS_{1000} neutrality	cond. tr. #1
7 Nov.	CS_{1000} neutrality	cond. tr. #2
9 Nov.	CS_{1000} neutrality	cond. tr. #3
14 Nov.		cond. tr. #4
16 Nov.		cond. tr. #5
28 Nov.	ext. tr. #1 v.c. +100,+150, 0, +250 f.e.v. +150,+200,+50,+150	cond. tr. #6
29 Nov.		ext. tr. #1 v.c. +125,+75 f.e.v. +100,+50 cond. tr. #7
5 Dec.	asthma produced without presenting any CS.	cond. tr. #8
7 Dec.	CS_{o1} neutrality	
	CS_{o1} cond. tr. #1	cond. tr. #9
14 Dec.		cond. tr. #10
15 Dec.		ext. tr. #2 v.c. +50, +100 f.e.v. 0, 0 cond. tr. #11
19 Dec.		cond. tr. #12
21 Dec.	ext. tr. #2 v.c. +275,+125,+125 f.e.v. + 75,+ 25,+ 25	
	CS_{o1} cond. tr. #2	cond. tr. #13
17 Jan. 1961	CS_{o1} cond. tr. #3	cond. tr. #14
17 Jan.	CS_{o1} cond. tr. #4	cond. tr. #15

TABLE 1 continued

Date	CS_{1000}	CS_{400}
24 Jan. 1961	ext. tr. #3 v.c. +25, -125 f.e.v. 0 , -100	
	CS_{ol} cond. tr. #5	cond. tr. #16
24 Jan.	ext. tr. #4 v.c. -50,-175,-50 f.e.v. -75, -50,-50	ext. tr. #3 v.c. + 50,-225,-125 f.e.v. +175, +75, +50 cond. tr. #17
16 Feb.	ext. tr. #5 v.c.-50,+225,+75,+100 f.e.v.-50,+125,+50, +75	
	CS_{ol} cond. tr. #6	cond. tr. #18
16 Feb.	ext. tr. #6 v.c.-175,+100, +50 f.e.v.+125, +75,+125	ext. tr. #4 v.c. -50, +75, -50 f.e.v. +50,+150,+150

TABLE 2

Mr. B. Conditioning and Extinction Trials

Date	CS_{1000}	CS_{400}
28 Nov. 1960	- - - - - adaptation to apparatus - - - - -	
30 Nov.		cond. tr. #1
2 Dec.		cond. tr. #2
5 Dec.	cond. tr. #1	cond. tr. #3
7 Dec.	cond. tr. #2	cond. tr. #4
9 Dec.	cond. tr. #3	cond. tr. #5
16 Dec.		cond. tr. #6
23 Dec.	ext. tr. #1 v.c. 0 0 f.e.v. -150, -50	
	cond. tr. #4	cond. tr. #7
9 Jan. 1961	cond. tr. #5	cond. tr. #8
11 Jan.	cond. tr. #6	cond. tr. #9
12 Jan.	ext. tr. #2 v.c. +75, +75 f.e.v. +100,-100	
	cond. tr. #7	cond. tr. #10
13 Jan.	cond. tr. #8	cond. tr. #11
16 Jan.	cond. tr. #9	cond. tr. #12
17 Jan.	ext. tr. #3 v.c. -125,-125 f.e.v. -150, -50	
	cond. tr. #10	cond. tr. #13
18 Jan.	cond. tr. #11	cond. tr. #14
19 Jan.	cond. tr. #12	cond. tr. #15
23 Jan.	cond. tr. #13	cond. tr. #16

TABLE 2 continued

Date	CS_{1000}	CS_{400}
24 Jan.	ext. tr. #4	
	v.c. +250, +250, +150 f.e.v. +25, +125, -75	
	cond. tr. #14	cond. tr. #17
25 Jan.	cond. tr. #15	cond. tr. #18
26 Jan.	ext. tr. #5	
	v.c. -25, +25, -25 f.e.v. -50, 0, +275	
	cond. tr. #16	cond. tr. #19
30 Jan.		ext, tr, #1
		v.c. -50,-100, -200 f.e.v. +25,-175, -25
	cond. tr. #17	cond. tr. #20
10 Feb.	ext. tr. #6	ext. tr. #2
	v.c. =100, +175, +125 f.e.v. +175, +75, -25	-100, +75,-25 f.e.v. +100, +300, 0

TABLE 3

Mr. D. Conditioning and Extinction Trials

Date	CS_{1000}	CS_{400}
17 Oct. 1960	adaptation and CS neutrality - - - - - - -	
19 Oct.	----------------adaptation----------------	
24 Oct.		cond. tr. #1
2 Nov.		cond. tr. #2
28 Nov.		cond. tr. #3
30 Nov.		cond. tr. #4
5 Dec.	cond. tr. #1	cond. tr. #5
7 Dec.	cond. tr. #2	cond. tr. #6
16 Dec.	cond. tr. #3	cond. tr. #7
19 Dec.	cond. tr. #4	cond. tr. #8
11 Jan. 1961	cond. tr. #5	cond. tr. #9
13 Jan.	ext. tr. #1 v.c. +200, +250 f.e.v. +300, +250 cond. tr. #6	
18 Jan.	cond. tr. #7	cond. tr. #10
23 Jan.		cond. tr. #11
25 Jan.	ext. tr. #2 v.c. -125, +225 f.e.v. +300, +200 cond. tr. #8	cond. tr. #12
27 Jan.	ext. tr. #3 v.c. 0, +75 f.e.v. +75, +125	ext. tr. #1 v.c. +50, +225 f.e.v. +150, +200

TABLE 4

Mr. M. Conditioning and Extinction Trials

Date	CS_{1000}	CS_{400}
25 Oct. 1960	- - - - adaptation and neutrality - - - -	
27 Oct.	- - - - - - - adaptation - - - - - - - -	
1 Nov.		cond. tr. #1
3 Nov.	CS_{1000} neutrality	cond. tr. #2
8 Nov.	CS_{1000} neutrality	cond. tr. #3
11 Nov.		cond. tr. #4
15 Nov.		cond. tr. #5
17 Nov.	CS_{1000} neutrality	cond. tr. #6
22 Nov.		cond. tr. #7
29 Nov.		cond. tr. #8
1 Dec.		cond. tr. #9
8 Dec.	CS_{o1} neutrality	
	CS_{o1} cond. tr. #1	cond. tr. #10
9 Dec.		cond. tr. #11
14 Dec.	CS_{o1} cond. tr. #2	cond. tr. #12
15 Dec.	CS_{o1} cond. tr. #3	cond. tr. #13
20 Dec.	CS_{o1} cond. tr. #4	cond. tr. #14
20 Dec.		ext. tr. #1 v.c. -100, -100 f.e.v. -25, -75
		cond. tr. #15
22 Dec.	CS_{o1} cond. tr. #5	cond. tr. #16

TABLE 4 continued

Date	CS_{o1}	CS_{400}
23 Dec.	ext. tr. #1 v.c.+225,+375,+575,+575 f.e.v. +75, +75,+175, +75	ext. tr. #2 v.c.+150,-150,-200,+50 f.e.v.+100, 0,-100,+50
11 Jan. 1961	ext. tr. #2 v.c.-200,-300,-500, 0 f.e.v.-125,-125,-175,-125	cond. tr. #17
13 Jan.		ext. tr. #3 v.c.+275,+325,+425 f.e.v. +75,+125,+125
	ext. tr. #3 v.c.-350,-300 f.e.v. 0 , 0	ext. tr. #4 v.c.+100,+325 f.e.v. 0, -50
17 Jan.	ext. tr. #4 v.c.-125,-275, -25 f.e.v. 0,-100, -50	ext. tr. #5 v.c.-50,+150,+350 f.e.v.+75,+100,+100
18 Jan.	cond. tr. #6	cond. tr. #18
23 Jan.	(CS_{o1} accidentally associated with a rise in vital capacity)*	cond. tr. #19
24 Jan.		ext. tr. #6 v.c.+100,+100,+150 f.e.v. 0, +25,+100 cond. tr. #20
25 Jan.		ext. tr. #7 v.c.+125,xxx, 0 f.e.v.+100,xxx,+50

* On this trial, a conditioning trial with CS_{400} and Isuprel was given first. While the vital capacity was still rising in response to the Isuprel, a conditioning trial was attempted with CS_{o1} and mecholyl. However, the protective effect of the Isuprel prevented any asthmatic response, and thus CS_{o1} was accidentally associated with asthma relief, constituting a counter-conditioning trial for CS_{o1}.

TABLE 4 continued

Date	CS_{o1}	CS_{400}
25 Jan.	cond. tr. #7	cond. tr. #21
26 Jan.	ext. tr. #5 v.c. -50, +75 f.e.v. -50, +25	ext. tr. #8 v.c.-175,-200 f.e.v. 0, *50

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ABSTRACT OF DISSERTATION

This study used the procedures of classical conditioning to investigate the possibility of producing asthmatic bronchospasm as a conditioned response. In order to carry out this study equipment was developed which permitted the experimental operations to be carried out while disguising the purpose of the experiment from the subjects.

In the experiment, bronchospasm, induced by inhaled acetyl beta methacholine chloride, and shown to be highly similar to the condition of the lungs in asthma, was paired with auditory or visual stimuli. Similarly, Isuprel-induced relief of bronchospasm was paired with another exteroceptive stimulus in an attempt to condition the end of the attack. Subjects, on the average, received ten to fifteen conditioning trials depending on their cooperation and availability.

Of four subjects who completed the necessary trials evidence for conditioning appeared in two. Magnitude of the conditioned responses is not great, producing, on the average, reduction of about 8% of the vital capacity in five minutes. Both of these subjects show conditioning to the experimental situation; one of the two, conditioning to the exteroceptive stimuli presented by the experimenter.

The fact that conditioning did not automatically result from the experimental procedure and the complexity of the conditioning process apparent from detailed examination of the individual cases, led to discussion concerning the nature of conditioning, with special emphasis on the new area of interoceptive conditioning. The author takes the viewpoint that a central emotional-expectancy is an important aspect of conditioned visceral responses, and rejects connectionism between an external stimulus and a response.

In addition, one peculiarity of the conditioning done in this experiment is noted. The unconditioned stimulus, rather than acting on the sensory nervous system, produces direct local change in the lungs. The resulting lack of representation of the UCS in the central nervous system is discussed in reference to classical Pavlovian theory.

The writer sees the application of interoceptive conditioning techniques as a fruitful method for further exploration of psychosomatic disorders.

AUTOBIOGRAPHY

The author was born in Boston, Massachusetts on December 9, 1931, son of Hiram and Irene Sloanaker. He attended the Belmont public school system and Harvard College receiving an A.B. degree in 1953.

From 1953 to 1955 he served as a line officer in the United States Navy, and returned to graduate studies, receiving the M.A. degree in psychology from Boston University in 1956. While preparing for the Ph.D. degree in clinical psychology in 1962, he was a trainee at Massachusetts General Hospital and Massachusetts Memorial Hospital. He also was a lecturer in psychology at Massachusetts Institute of Technology in 1958, and an instructor at the Boston

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