SODIUM AMYTAL AND EYELID CONDITIONING*

By

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INTRODUCTION

SODIUM amytal has long been regarded as a physiologically inhibiting drug. It is widely used in clinical practice as a sedative and sleep-producing drug, although all of its precise pharmacological effects are not definitely established. It has also been suggested that sodium amytal produces an increase in extraversion, as manifest by an increase in communicativeness, etc. Thus Lindemann (1932) found that after receiving amytal, normal subjects report feeling of increased well-being, co-operativeness, serenity and friendship. Sodium amytal is also used for the reduction of manifest anxiety. Sargant and Slater (1954) cite many examples of its use for this purpose with neurotic subjects; they describe it as useful for "deconditioning to situations likely to produce anxiety". Masserman (1938) reports that amytal apparently reduces the sympathetic activity in cats which normally results from faradic stimulation from the hypothalamus. It has also been shown to abolish conditioned fear responses in kittens (Bailey and Miller, 1952).

The literature related to conditioning is enormous. Hilgard and Marquis (1940) alone have a 973 item reference list at the end of their book. It has been established that anxiety neurotics or anxious subjects condition better than normals (e.g. Welch and Kubis, 1947a, 1947b; Taylor, 1951; Spence and Taylor, 1953; Spence and Farber, 1953). In the terminology of Eysenck (1952, 1953), in which introversion–extraversion and neuroticism are two orthogonal dimensions, anxiety neurotics are part of the groups known as Dysthymics, i.e. they have high scores on both the introversion end of the introversion–extraversion dimension and on the dimension of neuroticism. On the other hand hysterics and psychopaths have been shown to have high scores on the extraversion end of the introversion–extraversion dimension and on the dimension of neuroticism. Figure 1 will make this clear.

HYSTERICS Hysterics Psychopaths	Neuroticism	DYSTHYMICS Anxiety States Obsessive Compulsives Reactive Depressives
Extraversion		Introversion

FIG. 1.—The Orthogonal Dimensions of Introversion–Extraversion and Neuroticism.

It is possible that anxiety states could condition well because they are introverted or because they are neurotic. It is possible to investigate these

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possibilities by a critical experiment. If conditioning is related to neurosis then hysterics, psychopaths and dysthymics all condition well; if conditioning is related to introversion, then only the dysthymics should condition well and the hysterics and psychopaths should condition poorly. This experiment has been carried out and it was found that conditionability is related to introversion–extraversion and not to the degree of neurosis (Franks, 1955a). This finding is an elaboration of a profound observation by Pavlov (1927, p. 397f) made over a quarter of a century ago and largely neglected ever since. He postulated that hysterics possessed an exaggeration of the "inhibitory process" and that neurasthenics had an exaggeration of the "excitatory process". Since he had also established that dogs with an exaggeration of the inhibitory process conditioned poorly and that dogs with an exaggeration of the excitatory process condition readily it is possible to predict that hysterics should condition poorly and that anxiety states should condition readily.

It would seem possible, therefore, that on a more fundamental level both introversion–extraversion and conditionability are related to the cortical processes of excitation and inhibition, as conceived by Pavlov (1927, 1928, 1941). If this is so, then a drug which increases cortical inhibition should decrease conditionability and increase extraversion. One of the effects of sodium amytal would seem to be that of a cortical depression. Hence it may be predicted that this drug would reduce conditionability* and increase extraversion. As far as the present writers are aware this hypothesis has not been previously tested, although it has been shown (Hilgard and Marquis, 1940, p. 119) that other depressants, such as sodium bromide, retard the rate of conditioning and accelerate the rate of extinction.

Sample

The present study was carried out upon 16 neurotic hospitalized subjects, of either sex, diagnosed as dysthymics (anxiety states, obsessive compulsives, reactive depressives) and therefore expected to condition readily. Care was taken to exclude subjects who had, over the week preceding testing, been receiving barbiturates as a nightly sedative and subjects who were known to have any kind of brain injury. Subjects with any suspicion of psychotic traits were also excluded. All of the subjects were between the ages of 17 and 46 and none were of dull intelligence. Unlike a previous study in conditioning (Franks, 1954, p. 173–188) no attempt was made to reject those patients who had tendencies towards extraversion, as measured by the attainment of a critical score of 33 on a questionnaire test of extraversion, namely Guilford's R scale (Guilford and Guilford, 1939).

Treatments

Four different treatments were used, two of these consisting of different doses of amytal, one of a placebo and one of no drug or placebo. The problem of dosage has been considered by Goodman and Gilman (1941) who conclude

* Another effect of sodium amytal is to reduce the sympathetic activity of the autonomic nervous system. Now Spence and his colleagues (Spence and Taylor, 1951; Taylor, 1951; Taylor and Spence, 1952), proceeding within a framework of Hullian theory assume that conditionability is a function of total drive (D) and that variations in manifest sympathetic anxiety really reflect differences in this drive level. Using this theory it is also possible to predict that amytal would reduce conditionability. A way of evaluating the two theories would be to compare the effects of drugs which—as far as is possible—affect the autonomic nervous system only or the cortex only.

that "when barbiturates are injected intravenously it is difficult to judge in advance the amount to be given . . . reliance cannot be placed on fixed doses based on age and weight . . . individuals vary in their response" (p. 85). Because of this it was thought necessary to compare the effects of two different doses of the drug, one sufficiently large so that one could be reasonably certain of a definite clinical effect, and an appreciable smaller dose such that while marked clinical effect might not be readily apparent some effect could still be expected during the testing and clinical observation. There is some published guidance as to the magnitude of dosage required for these purposes. For example, Thorner (1935) found that 7·5 grains injected intravenously over a period of 4–5 minutes produced narcosis in two large groups of mentally sick subjects. His subjects comprised many kinds of diagnoses, including neurotic, psychotic and organic states. Among other findings was that patients with organic brain damage required smaller doses of amytal for narcosis to appear. Personal experience with drugs by the medical author of this paper suggests that a dosage of a ½ grain per stone body weight in dysthymic type of patients is most likely to produce the desired effects without producing sleep. It was therefore decided that the four different treatments of the present study would be constituted as follows:

(A) A large dose of intravenous sodium amytal. 0·5 grains per stone body weight, made up in a solution of sterile water immediately prior to injection, 1 grain of amytal being dissolved in 2 c.cm. of water, and injected into the right arm at the rate of 2 c.cm. per min. (i.e. at a rate of 1 grain per minute).

(a) A smaller dose of intravenous sodium amytal. This dose was always 2 grains less than the larger dose would be for that subject, made up and injected as above.

In practice the dosage range for the 16 subjects varied from 4 to 6 grains for "A" and from 2 to 4 grains for "a".

(P) A placebo injection of distilled water. This was injected in precisely the same manner and under the same conditions as the sodium amytal. A placebo injection was included in the experimental design since it has been suggested (Lewis, 1941, p. 271) that much of the effects of intravenous barbiturates is suggestive in origin.

(N) No injection at all.

More than one treatment and testing session should be allocated to each subject so that treatment comparisons can be made within each person. For administrative reasons only two sessions were allowed, the second session taking place 5 to 7 days after the first. Care was taken to ensure that at no time was the subject given any indication of which treatment he was about to receive or had received (except in so far as the subject was naturally aware that he was receiving neither drug nor placebo). The participation of the subjects was voluntary, and they were told that the purpose of the investigations was to discover whether the unknown drug would help them to relax or not.

PROCEDURE

The procedure was as follows: The subject was placed on a couch in a nearby room and the appropriate treatment administered. The subject was then taken into the sound-proof conditioning laboratory (Franks, 1955b) and exactly seven minutes were allowed to elapse between the withdrawal of the needle and the start of the conditioning session. As well as standardizing the

experimental situation this time interval allowed the subject to become acclimatized to the sound-proof conditioning laboratory and allowed the experimenters time to adjust the conditioning apparatus, etc. After the conditioning session was completed—approximately 25 minutes—the subject was given a brief interview. The questions asked included such items as "Did you feel sleepy?" "Was it hard to keep still?" The subject was also asked questions concerning how he felt, what effects he thought the drug had upon him, whether he felt conditioned (so phrased that the subject was not helped to realize the nature of the study, if he did not already know) and what his reactions were to being enclosed in this sound and daylight proof room.* The subject was then asked to sort certain personality questionnaires of Guilford (1940). Included in these personality scales were the Rhathymia scale (R), the Socal Introversion scale (S), Depression scale (D) and the Cycloid Disposition scale (C). According to Guilford the R scale differentiates the habitually gloomy individual from the cheerful and optimistic; and the C scale differentiates the individual with strong emotional fluctuations from the person with an even disposition and stability of mood. Eysenck (1953, p. 107) considers that D and C are largely measures of a personality factor of general neuroticism and that R is largely a measure of extraversion. The method of administration was different from that used by Guilford. Each item was typed on a separate card and the subject had to "post" these cards into one of three boxes labelled YES, ?, and NO. Finally the subject was given the Maudsley Medical Questionnaire, which consists of 40 "neurotic" items and 18 Lie scale items. Eysenck (1952, p. 94ff) discusses this questionnaire extensively and concludes that, given good subject motivation, it differentiates between neurotics and normals very well.

The sound-proof conditioning laboratory and conditioning procedure has been described in detail elsewhere (Franks, 1954). It is sufficient to state here that the unconditioned stimulus was a puff of air, delivered to one eye at a pressure of approximately 65 mm. of mercury from a distance of 2 cm. from the eye and lasting 500 milliseconds. The conditioned stimulus was a pure tone of frequency 1,100 cycles per second at an intensity of 65 dB above the subject's auditory threshold (which was first ascertained in the usual manner). The duration of this tone, heard through a pair of padded earphones, was 800 milliseconds. The air puff was so arranged that it began 350 milliseconds after the tone had commenced. Partial conditioning was used, the sequence being such that the reinforcement ratio was approximately 60 per cent. throughout the reinforcement trials. Thirty reinforcement trials were given, interspersed with 18 test trials, consisting of the conditioned stimulus alone. The inter-trial interval varied from 20 to 30 seconds with a mean of approximately 25 seconds. After the 30 reinforcement trials and 18 test trials (called acquisition test trials) had been given the subjects were given a further series of 10 consecutive test trials (called extinction test trials) so that the resistance to extinction could be measured. Throughout the conditioning session the subject sat in a comfortable arm chair with his head on a padded head rest and his feet on a foot rest. As well as being in a sound proof room, the subject was partially enclosed by a small booth, so that his field of vision was almost completely confined to this booth. All stimuli were administered and controlled electronically, the eyelid movements being measured by means of a photoelectric cell

* The clinical behaviour and body movements of each subject were also recorded. An analysis of these, together with the replies to the various questions asked is to be discussed in another paper (Laverty and Franks, 1955) which deals more specifically with the psychiatric aspects of sodium amytal effects.

(Franks and Withers, 1955). The occurrence of both stimuli and responses was registered on a recording milliameter.

Experimental Design and Analysis

Since there are four treatments (A, a, P and N) and only two testing sessions a rather complicated experimental design had to be adopted. This is the so-called "incomplete block" (Cochran and Cox, 1950, Chapter II). It is possible to obtain a balanced design using only six subjects (A–a; A–P; A–N; a–P; a–N; P–N), but since for each person test and retest data may differ, this basic design must be repeated, with each pair of treatments (e.g. A–N) in the reverse temporal order (e.g. N–A). Allocation of 12 patients to the 12 pairs of treatment combinations was at random, by means of a table of random numbers.

In addition it was thought worthwhile at this pilot study stage to examine the effects of giving the same treatment at both sessions. Therefore four patients (chosen at random from the initial 16) were given treatment combinations A–A, a–a, P–P and N–N. This subsidiary design can be treated separately from the main experiment and requires no very formal analysis at this stage.

It must be stressed that the experiment is conceived very much as a pilot study, on the one hand to test the main hypothesis (that sodium amytal reduces conditionability and increases extraversion) and on the other hand to give some general information and suggestions upon which more intensive investigations may be based. The experiment was kept so small that even the main hypotheses were unlikely to be confirmed (if true) at a very high level of significance, it being thought wasteful to expend the necessary labour to achieve possible significance with no knowledge of the factors involved.

The basic method of the formal analysis is that of analysis of variance. It is more complicated than for a straightforward design, however, since each subject receives only two of the four possible treatments. Yates's original method of analysis was adopted (see, for example, Cochran and Cox, 1950, pp. 324–25) in which the "treatments" sum of squares and the estimates of the treatment effects have to be specially "adjusted". The analysis of variance gives a residual error variance upon which tests of significance can be based.

The adjusted means (H) for each treatment are calculated from the straightforward means for each of the four treatments by an "adjustment" which allows for the individual differences between persons (since any one person is only given two of the four treatments). The appropriate error variance for a t-test comparing various adjusted treatment means is given in the present instance by ½ (Residual Error Variance in the Analysis of Variance).* If "between persons", i.e. individual differences are insignificant, then adjusted treatment and straightforward treatment will, of course, not differ significantly, therefore either could be used for further analysis. For convenience, the adjusted treatment will be used throughout.

* Cochran and Cox (1950, p. 325).

$$\text{Effective Error Variance} = \text{Residual Error Variance} \times \frac{k(t-1)}{t(k-1)} \times \frac{2}{r},$$

where k = number of readings per person;
t = number of treatments;
r = number of times each treatment occurs.

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RESULTS

1. *Conditioning*

TABLE I

Number of Conditioned Responses During Acquisition

Treatment	Adjusted Treatment Mean (H)
A	2·0
a	4·0
P	7·2
N	7·9

The analysis of variance failed to reveal any significant F ratios. The adjusted treatment means are presented in Table I. The residual error variance is 12·0, giving an Error Variance of 6·0 which may be used for testing the primary hypothesis that sodium amytal reduces the number of conditioned responses, i.e. that H_A is significantly less than H_N. Using a 1-tailed t-test this is confirmed at the 2·5 per cent. level of significance (the insignificant overall F test for the general treatments effect shows that none of the other treatment comparisons can be significant and therefore they should not be tested).

When the number of conditioned responses obtained during the extinction trials are analysed (Table II) both treatment and persons F ratios are found to be significant at the 5 per cent. level. The test-retest F ratio is not significant.

TABLE II

Analysis of Variance of Conditioned Extinction Responses

Source of Variation	df	Sums of Squares	Mean Squares	F	P Per cent.
Treatment	3	40·13	13·38	5·82	<5
Persons	11	105·83	9·62	4·18	<5
Test-retest	1	1·5	1·5	—	—
Residual	8	18·37	2·3	—	—
Total	23	165·83			

The adjusted treatment means for the extinction data are presented in Table III.

TABLE III

Number of Conditioned Responses During Extinction

Treatment	Adjusted Treatment Means (H)
A	0·1
a	1·9
P	3·8
N	3·9

When t-tests are carried out as before on the differences between the adjusted treatment means it is found that H_A is significantly less than H_N (2·5 per cent.), or H_P (2·5 per cent.). There is no significant difference between H_A and H_a or between H_N and H_P.

The correlation between the number of acquisition conditioned responses and the number of extinction conditioned responses is high and positive (·79). This is in agreement with earlier results (Franks, 1954, p. 261), using the same techniques, apparatus and similar subjects. It is considerably different from the

results obtained from Humphreys (1943), who found that acquisition and extinction scores for the eyelid reflex were not highly related.

The conclusion from the analysis of acquisition and extinction conditioned response frequencies so far is that sodium amytal apparently reduces the number of conditioned responses during both acquisition and extinction. Despite the high correlation between acquisition and extinction measures, the data suggest that as far as eyeblink conditioning is concerned resistance to extinction appears to be a more sensitive measure of the effects of sodium amytal than is the number of acquisition conditioned responses. No significant differences between the two dosages were obtained, but the trends in the adjusted means for both acquisition and extinction data are consistent with the possibility that conditionability is some undetermined negative function of the size of the dose administered. This finding may be obscured by both the small number of cases studied and the small difference in size between the two doses used. Interpretation of the data is also complicated by the possibility that different intensities of barbiturates may have different physiological effects (Brazier and Finesinger, 1945).

There were no significant differences in conditionability between subjects receiving a placebo injection and those receiving nothing at all, so that, as far as conditioning is concerned, the effects of sodium amytal cannot be considered due to suggestion.

The results for the 4 persons given the same treatment at each session are presented in Table IV.

TABLE IV

Conditioned Responses When the Subject is Given the Same Treatment Twice

Treatment	Average Number of Conditioned Responses: Acquisition	Extinction
A–A	5	1
a–a	12	1·5
P–P	15	7·5
N–N	14·5	8

These results are in agreement with the above conclusions. The fact that the general level of responding is higher than in the main experiment is most probably a result of random selection of subjects since this higher level of responding occurs in the first testing session as well as in the second.

TABLE V

The Relation of Treatment Effects to Rest-Retest

	Acquisition		Extinction	
	Session 1	Session 2	Session 1	Session 2
Mean Number of Conditioned Responses for A or a	3·7	3·7	1·5	1·0
Mean Number of Conditioned Responses for P or N	4·7	10·2	2·8	4·3

The relation of treatment effects to test-retest was investigated in the form suggested by the data, namely by comparing all A and a effects on session 1 with all A and a effects on session 2 and similarly for P and N. As Table V

suggests the expected* increase in conditioning from test to retest under treatments P and N is not apparent when the subjects receive amytal. This tendency is evident for both acquisition and extinction conditioned responses. Rough tests of significance based on the direct scatter of each set of 6 readings of which these are the means show that for both acquisition and extinction responses the P and N second session means are significantly greater than the other three means which obviously do not differ appreciably among themselves.

In assessing the likelihood of this effect being real or spurious it must be remembered that the sample is very small. A future experiment will therefore be required to confirm the existence of this effect. If confirmed, it may mean that amytal has no direct effect on conditioning, but only restricts the usual retention effects which appear in the retest situation. The possibility that sodium amytal has a cumulative effect here, reducing the ability to form conditioned reflexes upon the second session, is unlikely because the low scoring on the second testing under amytal occurred whether or not the patients had received amytal during the first session.

2. *Introversion–Extraversion*

TABLE VI

Effect of Treatment on Guilford's Scales S and R

Treatment	Adjusted Treatment Means (H)	
	Social Introversion (S)	Extraversion (R)
A	38·7	33·5
a	29·9	37·8
P	36·7	22·7
N	32·9	23·2

The analysis of variance, as expected, produces no significant test-retest F ratio for either social introversion (S) or extraversion (R) scales. The treatment F ratio is significant at the 1 per cent. level ($F=12\cdot0$) for the R scale. It is not significant for the S scale. When t-tests are carried out on the adjusted treatment means (H) of the extraversion scale scores (R), using the residual error variance (19·1) it is found that H_A is significantly greater than H_P or H_a ($p<0\cdot5$ per cent.). H_A and H_a do not differ significantly, neither do H_N and H_P. It would seem then that the hypothesis that sodium amytal increases the scores on Guilford's R scale measure of extraversion is confirmed although a corresponding decrease in social introversion (S) was not observed—possibly because S is not such a good measure of the dimension of introversion–extraversion as is R (Eysenck, 1953, p. 107). This need not necessarily mean that the subjects actually become more extraverted since it may be that they fail to answer the personality scale cards objectively when under the influence of amytal.†

The results for the four persons given the same treatment at each session are presented in Table VII.

* An increase of this order has been found in a study of normal subjects using the same apparatus and conditioning technique, but no injections (Franks, 1954, appendix No. 3, Table 20).

† In the authors' other paper (Laverty and Franks, 1955) the possibility that subjects tend to put more cards in the YES box under amytal is examined. The scales may be so framed that answering YES indiscriminately may have a differential effect on the final scores, affecting some scales, such as R, more than others. It is impossible, owing to the method of scoring used in the present study, to resolve this problem further.

TABLE VII

Scores on Guilford's S and R Scales when the Subject is Given the Same Treatment Twice

Treatment	Average S Scale	Score on R Scale
A–A	38	31
a–a	30	25
P–P	41	12
N–N	33	29

The data presented in Table VII are approximately in agreement with the above conclusions.

CONCLUDING SUMMARY

The two main hypotheses of this pilot study would seem to be confirmed tentatively. These are (1) that intravenous sodium amytal reduces the number of conditioned eyeblink responses during acquisition and increases the rate of extinction; (2) that intravenous sodium amytal increases the extraversion score as measured by Guilford's R scale.

These two conclusions must be regarded with caution and as requiring further experimental investigation, since the possibilities arise from the data that (1) sodium amytal has no direct effect upon conditioning but only restricts the appearance of the usual retention effects which manifest themselves during retest; (2) the increase in R score (extraversion) after the subject has received intravenous amytal may be, in part at least, a product of an increased tendency to say YES to the questionnaire items while under the influence of the drug.

For no measure were the scores obtained under treatment P (placebo injection) significantly different from the score obtained under treatment N (no injection), neither were any trends in the data evident. It would seem reasonable to conclude that, as far as eyelid conditioning and the personality questionnaires used in the present study are concerned, the effects of intravenous sodium amytal cannot be attributed to suggestion.

Under the conditions of the present study a dosage difference of 2 grains intravenously produces no significant differences in the measures under investigation. The trends in the data however are consistent with the possibility that eyelid conditionability is some undetermined negative function of the size of dose administered.

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