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LOBELINE AND REDUCTION OF CIGARETTE SMOKING[1]

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Summary.—An empirical and logical analysis of research employing lobeline sulfate in reducing cigarette smoking raises serious doubts as to the utility of this chemical "nicotine substitute." An experiment is also described in which predominantly college-aged volunteers desiring to stop smoking were given either specially prepared troches containing 0.5 mg. lobeline or placebos in a double-blind design. Neither during treatment nor during an immediately following post-treatment period did the drug achieve greater gains than the placebo. Correlational and other analyses of psychological data suggest that the local throat irritation commonly regarded as a side-effect of lobeline lozenges actually plays a central role in discouraging smoking in those persons motivated to continue sucking the lozenges. Suggestions are also offered as to procedures that might prove useful in maintaining treatment gains, whether drug-produced or part of the familiar placebo effect.

Two recent reviews provide excellent critical summaries of both clinical and experimental research on a wide variety of smoking-reduction techniques (Bernstein, 1969; Keutzer, Lichtenstein, & Mees, 1968), and we would agree with the general conclusions of these writers that there is *little evidence of specific treatment effects over and above the omnipresent placebo effect* in research on the reduction of cigarette smoking. The area which concerns us most directly here is that which utilizes lobeline sulfate as a smoking deterrent. Our presentation begins with an historical review of lobeline research in smoking, moving then to a controlled double-blind study conducted by the present writers, and ending with some theoretical and research considerations on the use of lobeline compounds in smoking-reduction research.

Review of Lobeline Research

Lobeline is an alkaloid originally derived from the leaves of an Indian tobacco plant (*Lobelia inflata*). Its therapeutic history dates from the early nineteenth century when it was used by Sir Samuel Thomson as an emetic (Wright & Littauer, 1937). In fact, the alpha-form of the drug, which is the currently approved form, affects the autonomic nervous system ganglia and the medullary system (London, 1963). In large doses it has resulted in marked respiratory changes, direct and indirect effects on the circulatory system, and in some cases vomiting—apparently as a result of stimulation of the vomiting center.

Because of its original derivation from a tobacco plant, as well as the apparently similar physiological effects to nicotine, Dorsey (1936) first attempted

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treatment of smoking by administering 8-mg. tablets of lobeline sulfate. Despite "acute discomfort" in many cases, Dorsey reported general effectiveness of the treatment procedure. However, this was in no sense of the word an experiment, rather a completely uncontrolled observation, without even a data report.

Other efforts followed. Still using an 8-mg. dosage, Wright and Littauer (1937) administered lobeline as a smoking substitute to 28 smokers. While these investigators improved on Dorsey's work by including a magnesium oxide control group, they still failed to report any data. Moreover, the drug produced such aversive gastric effects as to lead the authors to caution against its usage. A noteworthy comment of theirs was: "In the last analysis no substitution drug or product which will tide a patient over the period of transition from smoker to nonsmoker will prevent him from resuming the pleasant habit when it stopped."

Due to the considerable side effects obtained from large doses, most subsequent research has concentrated on smaller, buffered dosages. One noteworthy exception is the research performed in Ejrup's (1965) clinic in Stockholm. Ejrup worked on the "nicotine substitute" hypothesis and injected patients with Lobeline Hydrochloride up to saturation level. Once again dramatic (side) effects were reported: "Dizziness, nausea and vomiting, appearing 15—30 minutes after the injection when too large a dose was given or if the patient tried to smoke a cigarette" (p. 341). When it is so clear that the treatment may be worse than the disease, it seems most likely that decreases in smoking were merely a reaction to the very aversive consequences, as Ejrup included no control for this factor, and that no real "nicotine substitution" had taken place. This is borne out by the 70% relapse rate. As for lobeline sulfate in tablet form, Ejrup points out that the lobeline is not absorbed well, and he suggests that: "The effect of the tablets is more a local irritating effect back in the throat." This point will later be discussed in detail.

Lobeline preparations are commercially available in one of two forms: 2 mg. of lobeline sulfate with 100 mg. of antacid (Bantron), or .5 mg. of lobeline sulfate in a flavored, inactive base (Nikoban). While there is a paucity of evidence favoring either preparation, the relevant evidence will be reviewed separately. As our own investigation concerns the .5-mg. preparation, only a brief review of the studies with 2 mg. will be reported.

2 mg. Lobeline.—Rapp and Olen (1955) in a preliminary study comparing the Bantron preparation with a starch capsule placebo obtained very encouraging results during three treatment weeks with 200 *S*s. However, when another group of *S*s received either lobeline without the antacid base, or antacids without the lobeline, significant differences between groups failed to materialize. Thus, unless there is some unique effect of the lobeline plus antacid preparation, it seems that antacids alone could be just as effective as Bantron. Moreover, they report no post-treatment data at all.

Negative results were reported by Bartlett and Whitehead (1957). In a double-blind crossover design with 33 medical students not motivated to stop smoking, the number of cigarettes smoked in each condition over a 3-wk. period was recorded. The conclusion was: "No effect was noticed upon administration of meprobamate or a commercial buffered lobeline preparation" (p. 281).

Probably the most favorable results for the 2-mg. preparation were reported by Rapp, Dusza, and Blanchet (1959). They measured both the number of cigarettes smoked as well as the weight of tobacco consumed by 25 motivated and 25 unmotivated *S*s during one week of taking a starch placebo, as opposed to a week on Bantron. Although they report positive findings (i.e., superiority of lobeline over placebo), a major flaw in the study is their failure to counterbalance conditions: all *S*s first had the placebo and then the drug. If there were any cumulative effect of "being in treatment," then this factor would have completely confounded the results. *En passant* it is worth noting that a considerable number of lobeline studies have committed the same methodological error. Unless appropriate counterbalancing is provided for, the crossover design is totally inappropriate for this kind of research. A further problem in interpreting this study is their failure to report whether *S*s felt perceptibly different on control and Bantron weeks (were *S*s in fact blind?). As with most other studies, no post-treatment data are reported.

Edwards (1964), after obtaining completely negative results with a 3.5-mg. compound, concluded that: "The possibility that the technique of double-blind control has been inadequate in some of the previous studies is an explanation which must now presumably be entertained." Merry and Preston (1963) compared 2 mg. of lobeline to an antacid control and found no differences at all. Scott, *et al.* (1962), in a similar study, also failed to find significant differences between a lobeline and a control group.

Additional evidence against the 2-mg. preparation comes from a study done by the Research Committee of the British TB Association (1963). They gave 2-mg. lobeline sulfate tablets to 43 *S*s and placebos to 38 controls in a double-blind design. They measured smoking both during the 6 wk. of treatment and 6 wk. after treatment. During and after treatment the inert tablet placebos produced as much smoking reduction as the lobeline tablets. In their review, Ford and Ederer (1965) suggest that: "The duration of this trial, its double-blind design, and the fact that the patients had diseases in which smoking was contraindicated and had expressed a desire to stop are factors which lend support to the negative conclusion as to the usefulness of lobeline" (p. 141).

.5 mg. Lobeline.—Working on the hypothesis that lobeline achieves its effect through gastric hypomotility, London (1963) purports to show that .5 mg. of lobeline sulfate in a cherry flavored pastille (Nikoban) significantly suppresses craving for nicotine. Although London does not specify the details of the placebo used, it is unfortunate that he apparently did not use a control which

also effected gastric hypomotility, without producing the other alleged effects of lobeline. Particularly in view of the results of the Rapp and Olen (1955) study, which found antacids without the addition of lobeline as effective as the lobeline itself, any study which fails to use an *active* placebo of sorts can hardly produce any conclusive findings about the specific effects of lobeline.

There is a further problem with regard to the adequacy of London's control group. He reports that 59.5% of the lobeline group experienced oropharyngeal discomfort, whereas only 9.3% of the placebo group experienced the discomfort. This difference becomes particularly salient when one considers the relative proportion of *Ss* who reduced more than 50% during the treatment: 51.8% more lobeline than control *Ss* (almost exactly the same difference as reported discomfort between the two groups). London claimed to find a significant difference in smoking reduction between lobeline and controls at the 4th week of treatment, but the significance of the results might reflect either the extent to which the experimental group were "unblinded" or the degree to which continued irritation from the lobeline made smoking unpleasant. No post-treatment data were reported. The same criticism might be leveled at a study done by Rosnick (1965): his experimental subjects reported "a feeling of having smoked too much resulting largely from a sense of epigastric fullness."

Bachman (1964) attempted to evaluate the effectiveness of .5 mg. of lobeline sulfate by using a double-blind crossover design (with only 13 *Ss*). All *Ss* received the Nikoban on the 1st, 3rd and 5th weeks, and an unspecified placebo every 2nd, 4th and 6th weeks. As discussed above, although the results favored the lobeline preparation, this study is subject to the same major flaw as all the other crossover studies. As there is no report on the "activity" of the placebo, the obtained results could well be just due to *Ss*' ability to discriminate between lobeline and placebo weeks, particularly as they received such clear opportunities for successive comparisons. Furthermore there is a lack of detailed post-treatment data.

In a study lacking in adequate controls, Graff, *et al.* (1966) found that a drug which was nonspecific in relation to smoking (Chlordiazepoxide) produced significantly greater smoking reduction than lobeline both during treatment as well as over a 3-mo. follow-up. Moreover, they found that lobeline treatment fared significantly worse than hypnosis or group therapy. Further negative results were found by Leone, *et al.* (1968) in the Rhode Island Hospital program. Using Nikoban, they compared synthetic lobeline, natural lobeline and unspecified placebos in a double-blind design. They found no significant difference in the rate of withdrawal between lobeline and placebo users. *Ss* definitely found the lobeline preparation aversive.

Thus, in retrospect, there is precious little evidence available for the efficacy of lobeline as a smoking suppressant over a broad range of dosages and modes of administration. Moreover, data are notably lacking on the persistence of any

reductions observed during treatment. Ford and Ederer (1965), in a review of the research, concluded that: "It is apparent that the majority of controlled studies have not demonstrated that lobeline is superior to a placebo" (p. 121).

On the basis of the methodological inadequacies discussed above, any adequate demonstration of the effectiveness of a lobeline compound requires a design which fulfills the following experimental requirements: complete double-blinding; independent control group (the "crossover" design is inappropriate for the reasons discussed above); a group receiving an "*active*" placebo (mimicing the nonspecific effects of the drug as far as possible); post-treatment maintenance measurement of placebo as well as experimental *S*s.

The purpose of the present study was to satisfy the above requirements as far as possible in order to adequately test the effectiveness of the .5-mg. lobeline compound. In addition to testing the efficacy of the drug, however, we hoped also to pay more attention to some of the *psychological variables* which could be instrumental in increasing or decreasing smoking in the context of a drug therapy program. More specifically, we were interested in how *S*'s perceptions of the situation might influence the results both during and after lobeline treatment, i.e., in view of the reported aversive "side-effects" of the lobeline compound, we were interested in the irritation experienced by the subject in the drug as opposed to the placebo group, and how this might correlate with outcome. Also, insofar as the bulk of previous research reported negative findings for specific drug effects, it would seem that *S*'s perceived exercise of "will-power" might be expected to correlate to some extent with treatment gains. These as well as other possible psychological determinants of treatment effects were therefore investigated.

In addition to studying the psychological factors operative during the treatment phase, we were also interested in determinants of post-treatment maintenance. Post-treatment maintenance of smoking reduction is a notorious problem. Even the most rigorous of regimens result in a relapse rate as high as 70%. This can be viewed as an instance of a more general problem, that of the difficulty in transferring to the nondrug-state behavorial changes occurring under the influence of various psychoactive preparations. For example, Kamano (1966) concluded from his careful review of the psychiatric literature that, while many psychoactive drugs effect beneficial changes, patients tend to lose ground once the treatment is terminated, even when gradually. In the experimental animal area, Miller (1966) and his associates have found failure of fear-reduction from sodium amytal to transfer to the non-drug condition. Related issues have also been dealt with by Overton (1964) in his discussion of state-dependent learning. Contrary evidence is also available, however (Miller, *et al.*, 1957; Nelson, 1967), and it was hoped that our program of research would elucidate some of the variables involved in the maintenance of drug-induced behavior change.

A possible social psychological explanation for the problems in transfer of drug-effects has been advanced by Davison and Valins (1969). In brief, the

essence of their hypothesis is that *S*s who *attribute* their behavioral changes to a drug transfer these changes significantly less to the non-drug state than do *S*s who are deprived of this drug attribution and who, therefore, presumably believe themselves to have been importantly involved in changing their own behavior. According to the well-known "placebo effect," a drug's therapeutic efficacy is likely to be enhanced by the patient's "faith" in the drug. In contrast to this, however, the Davison and Valins (1969) "attribution" hypothesis suggests that from the point of view of post-treatment maintenance, it might not be to *S*'s advantage to believe that he had received an effective drug. To investigate the possible role of such post-treatment perceptions, this study therefore also included an independent manipulation of *S*s' belief in the strength of the drug they had received.

METHOD

Subjects

Volunteers were recruited through an advertisement in the campus newspaper. *S*s were members of both sexes from the university community who were offered the opportunity to participate in an experimental study investigating the effects of a commercially available chemical compound in reducing smoking. Of 34 *S*s 31 who volunteered completed the program.

TABLE 1
EXPERIMENTAL DESIGN

Actual Content of Pill	Post-treatment Information on Content of Pill	
	Disabuse	Control
Drug	$N = 8$	$N = 8$
Placebo	$N = 8$	$N = 7$

Procedure

At the first meeting *S*s were supplied with a pocketsized recording booklet in which they were instructed to record when they lighted each cigarette smoked for 1 wk. (baseline rate week) prior to the treatment period; it was felt that *S*s would be more likely to report numbers of cigarettes smoked if instructed to record the times they lit them. *S*s were encouraged to make this week as representative of their typical smoking behavior as possible, and the importance of accurate recording was emphasized most strongly.

The form of the treatment program was also explained at this time. In particular it was pointed out that it would be necessary for some *S*s to receive placebos in order to evaluate the efficacy of the drugs to be used. *S*s with reservations were urged to withdraw at this stage. Demographic and other general information were collected via questionnaires. Any *S* who had previously used commercially available smoking deterrents was not included. Our sample was not what could be properly described as "hard core," the mean age being 21 yr., with average duration of smoking less than 5 yr. The questionnaire data strongly indicated that there were no misconceptions about the nature of the program. On the basis of the number of cigarettes smoked over the initial period, *S*s were arranged into two matched groups, one group to actually receive the drug, and the other to receive the

placebo. The active drug consisted of .5 mg. of lobeline sulfate in a specially designed base. This cherry flavored base was intended to mask the typical burr of the lobeline as far as possible, and thus render the active drugs indistinguishable from the placebos, which consisted of the base alone without the lobeline sulfate.[2]

At the second meeting, after the base-rate recording week, all *Ss* received a 4-wk. supply of lozenges, to be taken according to the following regimen:

Week 1: One lozenge every 2 hr.—maximum of 10 per day.
Week 2: One lozenge every 3 hr.—maximum of 7 per day.
Week 3: One lozenge every 4 hr.—maximum of 5 per day.
Week 4: One lozenge every 5/6 hr.—maximum of 3 per day.

This schedule is recommended by the commercial distributors of Nikoban.

Following further the instructions issued with Nikoban, we urged *Ss* to exercise as much will-power as possible, and to attempt immediately to cease smoking entirely. During the following four treatment weeks, *Ss* were required to record any cigarettes smoked and to return record sheets at the end of each week. The entire experiment was double-blinded: the lozenges were coded at the outset by colleagues not connected with the program, and the code was not broken until all the data had been collected.

At the end of the 4-wk. treatment period all *Ss* met once again. At this meeting what was in effect the second phase of the experiment was begun. In order to investigate the possible effects that *Ss*' attributions of treatment-gains might have on the maintenance of those gains, half the *Ss* who had received the active drug were told that they had received the optimal dosage of the drug (Control), while the other half were told that they had received placebos (Disabuse). In like fashion, half of the *Ss* who had in fact been taking placebos were told that they had been taking the optimal dosage of the drug, while the other half were correctly informed that they had merely been getting placebos. This deception was deemed necessary to evaluate the independent effects of attribution manipulations.

RESULTS

Effects of Lobeline versus Placebo

Table 2 contains daily baseline, treatment, and post-treatment means for cigarettes smoked by *Ss* who were actually on either the 0.5-mg. lobeline pastilles or the placebos. Analysis of variance was used to assess the differences between groups across the repeated measures. It can be seen that our *Ss* were not exactly matched prior to treatment, but the mean of 19.8 cigarettes per day for Drug *Ss* is not significantly greater than the 17.1 cigarettes for the Placebo *Ss*. If one compares the two groups over the 4 wk. of treatment, it is clear that for 3 of the

TABLE 2

MEAN DAILY CIGARETTE CONSUMPTION

	N	Baseline	Treatment Week				Posttest
			1	2	3	4	
Drug	16	19.8	4.1	5.4	6.3	6.3	10.2
Placebo	15	17.1	2.8	4.0	5.1	6.5	8.5

[2]We are very grateful to Dean Joseph L. Kanig and his students of the Columbia School of Pharmacy for their generous co-operation in manufacturing the lobeline and placebo lozenges used in this study.

4 treatment weeks, Drug *Ss* were smoking slightly *more* cigarettes per day than were those sucking on placebos. The differences, however, do not approach significance. Another way to look at the treatment data is to ask what proportion of *Ss* achieved various percentage-reductions in their smoking. Table 3 shows no statistically significant differences on this measure as well between Drug and Placebo groups. Thus, one can conclude that it did not matter during treatment whether *Ss* were using the lobeline lozenges or the placebos.

TABLE 3
PERCENTAGE REDUCTION IN SMOKING: BASELINE MINUS WEEK 4/BASELINE

Group	*N*	Reduction			
		85-100%	50-84%	15-49%	< 15%
Drug	16	37.5	37.5	25.0	0.0
Placebo	15	33.3	33.3	26.7	6.7

Assessment of change from before to following treatment can be made in any number of ways, though it will be seen that no analysis yields a significant difference. A comparison of just the two post-treatment means (Drug: 10.2, Placebo: 8.5, see Table 2) yields no difference that is significant statistically. Since our two main groups did differ somewhat at baseline, we computed change-scores by subtracting post-treatment means from baseline means. Again, no significant difference is found. We then compared the increase in cigarettes from the fourth week of treatment to the post-treatment week, as a measure of "loss of treatment gains," but here also was no difference found; it is of interest, however, to note that Drug *Ss* increased an average of 4 cigarettes per day while Placebo *Ss* increased only 2 per day. In sum, none of the comparisons of the two main groups for maintenance of treatment-gains showed a significant difference between lobeline and placebo.

Attribution Results

In order to determine the effect of *Ss*' perception of possible treatment gains, it will be recalled that half of each group of *Ss* had been told that they had received a placebo ("disabuse"), while the other half were informed that they had received an optimal dosage of the active drug ("control"). From Table 4, which shows change-scores from baseline to the post-treatment week, it is apparent that

TABLE 4
MEAN CHANGE-SCORES (BASELINE MINUS POST) FOR 4 GROUPS IN A FACTORIAL DESIGN (NUMBERS OF CIGARETTES SMOKED DAILY)

Group	Disabuse	Control	*M*
Drug	11.8	7.4	9.6
Placebo	10.5	6.4	8.6
M	11.2	6.9	

the disabuse group showed an average improvement of 11.2 (fewer cigarettes smoked daily) as opposed to only 6.9 in the control group, thus appearing to indicate that *S*s who believed they had received an inactive drug showed substantially better maintenance than *S*s who believed they had received an effective drug.

However, the possible strength of this finding is diminished by Table 5, which shows that due to an unfortunate chance sampling distribution, at the end of Week 4 (prior to any information on the strength of drug they had been receiving), *S*s who were about to be "disabused" had by chance reduced their smoking a great deal more than *S*s who were in the "control" group. Indeed, when we compare Drug-Disabuse with Drug-Control *S*s on treatment effect (Baseline minus Week 4), a Mann-Whitney *U* test yields a difference which is clearly significant ($p < .04$, two-tailed test).

TABLE 5

BASELINE MINUS TREATMENT WEEK 4 (NUMBERS OF CIGARETTES SMOKED DAILY)

Group	Disabuse	Control	*M*
Drug	16.4	10.7	13.6
Placebo	12.6	8.3	10.6
M	14.5	9.6	

Thus, although we cannot really conclude that *S*'s believing that he had received an inactive drug produced significantly *better* maintenance, it is of interest that, contrary to the usual "placebo effect," it did not seem to have a damaging effect on the maintenance of treatment gains if *S* believed that he had merely been taking an inactive drug.

Correlational Data

It will be recalled that several questionnaires were filled out by *S*s during the study. Since we believe that our experimental setting maximized the chances of honest and conscientious reporting, we shall report several of these correlations which may be of interest to readers. Some of the results will be reported and discussed more extensively in the final section of the paper. All correlations, unless otherwise noted, are Kendall's *tau*, a nonparametric measure of degree of association recommended for data like ours. All probability levels are two-tailed unless otherwise noted.

Treatment-effect, as defined by the difference between Baseline and the fourth (final) week of treatment, correlated significantly and negatively ($p < .01$) with the number of times *S*s had tried to stop smoking in the past and with the number of years they had been smoking ($p < .05$). Expectation of help from smoking-deterrent drugs did not correlate with treatment-effect, nor did amount of will power *S*s believed they would be able to exercise; no significant

correlation was found between treatment-effect and expressed desire to stop smoking. All these measures had been taken prior to the baseline week of measurement.

A means-difference test was run between numbers of lozenges used throughout treatment (recall that *S*s could exercise discretion as to how many lozenges to use, up to specified maxima) for Placebo versus Drug *S*s, and no significant difference was found: Placebo *S*s used neither fewer nor greater numbers of lozenges than did those *S*s using the lobeline pastilles. In fact, the modal number of lozenges consumed in both groups closely approximated the maximum suggested dosages.

Discussion

While our data allow no meaningful conclusions regarding attribution and maintenance, we do feel that our lobeline and placebo data are valid, and it is clear that we have failed to demonstrate any differences at all in the use of a .5-mg. lobeline lozenge as compared to a placebo, in the context of a program for reducing smoking in motivated *S*s; this absence of differences was found both during the four treatment weeks and in pre- minus post-treatment change-scores. It must be borne in mind, of course, that one can never prove the null hypothesis, that is, we cannot conclude that such a lobeline lozenge has no effect; rather, we can only conclude that our study, like most others, has failed to show an effect over and above the placebo effect.

Even though no differences between lobeline and placebo emerged, it is logically possible that different factors operated in each group to produce the significant reductions that occurred in both groups. [It should be borne in mind (cf. Bernstein, 1969) that all treatment procedures appear to achieve reductions of from 50% to 70% over a comparable length of time.] The questionnaire data suggest some interesting hypotheses, which we report here, ever-mindful of the impossibility of drawing causal inferences from correlational data. The laboratory supplying our materials was not successful in masking the irritation caused by the lobeline: Drug *S*s rated their troches significantly more irritating than did Placebo *S*s ($p < .01$, two-tailed, Wald Wolfowitz test), though fortunately, Placebo *S*s did not, on the average, believe they were not taking an actual drug. As might be expected, degree of throat irritation correlated significantly and positively with how strong a dosage *S*s thought they were getting ($p < .02$). In addition, perceived strength of dosage predicted the treatment-reduction for Drug *S*s ($p < .04$) but not for Placebo *S*s. All this suggests that Drug *S*s reduced their smoking rate at least partly due to the irritation caused by the lobeline troches which they committed themselves to taking.[3]

[3]It will be noted that, as with the earlier studies we have critiqued, we did not succeed in making the lobeline lozenges indistinguishable from placebos, that is, it was significantly more uncomfortable to suck the drug lozenges than the placebos. It is possible, therefore, that our *S*s were "unblinded" to a degree. Our questionnaire data, however, do indicate

Why, then, did the Placebo *Ss* cut down, assuming that throat irritation was important only for the treatment effect observed in the Drug *Ss*? It will be recalled that all *Ss* were urged to "try" very hard not to smoke while using the lozenges. *Ss* were required to check the appropriate point on a linear rating scale to indicate how much "will power" they felt they had exerted during treatment. Examination of these will power ratings shows that Drug and Placebo *Ss* did not differ on the degree of will power which they believed they had exerted during treatment, and both groups did report themselves, on the average, to have exerted significant degrees of will power. Correlations were then run between will power and treatment-effect for each group, but in neither case was the correlation significant. Thus, although the lobeline lozenges produced minor throat irritation this appeared to be the only respect in which different treatment effects were reported by the Drug group. While this reported aversiveness did not result in over-all greater smoking reduction during the treatment period, it is conceivable that the Drug group achieved the same reduction in a somewhat different manner from the Placebo group.

These considerations lead further into the presumed mode of action of lobeline sulfate. Our historical review shows that it was initially viewed as a substitute for nicotine—both because of its derivation from tobacco plants and from the nicotine-like physiological effects produced by its ingestion. This "nicotine substitute" hypothesis has guided virtually all lobeline smoking research. Furthermore, while the unpleasant side-effects of varying dosages of lobeline have been duly noted by many investigators, ranging from vomiting to throat discomfort, these symptoms have generally been viewed as having only nuisance-value. The makers of Nikoban, for example, caution the consumer about possible throat irritation but term it as a temporary side-effect which should be *disregarded.* It may be, however, that this laryngeal discomfort contributes to the treatment-effect in those smokers who are committed enough to endure the irritation.

We must ask now what evidence there is that cigarette smokers continue to smoke because their bodies crave nicotine. There seem to be two separable aspects to this problem. One is the question of physiological addiction: Can regular smokers be regarded as *addicted* to nicotine? We tend to agree with Bernstein's (1969) conclusion that they cannot be so regarded, assuming a strict construction of addiction as involving physical dependence on nicotine with a compulsion for increasing dosages and a characteristic pattern of somatic complaints during withdrawal aside from those that typically accompany any emotional disturbance.

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that our placebo *Ss* did not believe they were not getting a real drug. But perhaps more importantly, our study did *not* show a superiority of lobeline over placebo, thus rendering irrelevant—for double-blind purposes—the fact that our lobeline lozenges were irritating to the throat where our placebos were not. If we had, in fact, found a true drug-effect, the criticism we have already raised with earlier research regarding throat discomfort from lobeline would be important.

But even if regular cigarette smokers cannot (yet) be construed as true addicts, it is logically possible that they do crave nicotine, that is, that, for whatever reasons, they seek after the somatic effects that the nicotine in cigarettes reliably produces. If this is the case, then lobeline, in the range of dosages currently used generally, might with good reason be seen as a valuable substitute for the craved nicotine. But what is the evidence for "nicotine hunger?" In introducing a well-controlled study of their own, Lucchesi, Schuster, and Emley (1967) review several earlier uncontrolled clinical reports describing either the injection or oral ingestion of varying dosages of nicotine by cigarette smokers who, until the drug was metabolized, tended to smoke far fewer cigarettes than normal (e.g., Finnegan, *et al.*, 1945; Johnston, 1942). Lucchesi, *et al.* themselves administered intravenously to smokers unmotivated to stop and unaware of the true purpose of the experiment varying concentrations of nicotine interspersed randomly with saline; with the needle in place, *S*s were free to smoke, and the dependent measure was number of cigarettes smoked (as well as the weight of unsmoked tobacco) during nicotine periods as contrasted with control periods. A first experiment failed to find differences when 1 mg./hr. of nicotine was administered over a 6-hr. period. When this dosage was increased to 2 mg. for the first hour and 4 mg./hr. for the next 5 hr., significant differences did emerge: *S*s smoked significantly fewer cigarettes while on saline.

It should be noted, however, that *S*s still smoked a good deal, at no time decreasing more than 60% over control periods. That this was a weak effect of the nicotine injections was duly noted by the authors. They then pointed out that the smoke actually inhaled by the average smoker from one cigarette contains between 1.2 and 3 mg. of nicotine; thus their effective dosage of 4-mg. nicotine injected per hour was roughly equivalent to two cigarettes per hour. As they conclude: "The results obtained suggest that nicotine plays a small but significant role in the smoking habit and that part of the craving for a cigarette can be satisfied by the intravenous administration of the alkaloid . . . if the pleasure of smoking or craving for tobacco were due to the general effects of the alkaloid we should have observed a much greater reduction in the smoking frequency" (p. 795).

It appears, then, that in addition to absence of evidence that smokers are physically addicted to nicotine, their smoking can only partially be seen as a function of nicotine hunger. But there is an additional problem as far as lobeline is concerned, namely, what evidence is there that the "nicotine substitute" properties of, at most, .5-mg. lobeline every 2 hr. (Nikoban, as in our study) or, at most, 2-mg. lobeline every 5 hr. (Bantron) function even in the relatively weak way that 4 mg./hr. of nicotine was shown to work in the Lucchesi, *et al.* study? We have been unable to find any such direct evidence of this crucial aspect of the logic underlying the expectation that commercially available lobeline preparations will satisfy the smoker's craving for nicotine and thereby markedly reduce his use of cigarettes.

Since the nicotine substitute hypothesis seems doubtful, what implications do our "discomfort" speculations have for maintenance of treatment-gains? As we have documented, no lobeline treatment extant has been shown to satisfactorily reduce or eliminate smoking over the long-term (e.g., 3 mo. and longer). If such procedures work because they render smoking less enjoyable or even aversive, on what grounds would one expect such reductions in smoking to be maintained once the drugs have been discontinued? Common sense would seem not to predict maintenance—"I am no longer sucking/swallowing what has made my cigarettes taste awful, so I may now smoke with pleasure once again." A more sophisticated analysis would seem to lead to the same prediction: although numerous animal experiments in aversive conditioning demonstrate enduring effects of repeated pairings of an aversive unconditioned stimulus with a neutral or positive stimulus (e.g., Gantt, 1944), such long-term effects are singularly lacking with human beings (Davison, 1969).

No single experiment ever settles an issue, least of all a study which fails to demonstrate differences. So we would consider it a little premature to assert that a product like Nikoban is nothing more than a placebo. Nonetheless, our negative results are not inconsistent with those few earlier studies which contained fairly satisfactory controls, and we do believe our design and procedures provided reasonable opportunity for differences to emerge if 0.5 mg. lobeline sulfate in a candy base is anything more than an expensive placebo.

REFERENCES

BACHMAN, D. S. Group smoking deterrent therapy. *General Practice*, 1964, 30, 86-89.

BARTLETT, W. A., & WHITEHEAD, M. D. The effectiveness of meprobamate and lobeline as smoking deterrents. *Journal of Laboratory and Clinical Medicine*, 1957, 50, 278-281.

BERNSTEIN, D. Modification of smoking behavior: an evaluative review. *Psychological Bulletin*, 1969, 71, 418-440.

BRITISH TUBERCULOSIS ASSOCIATION. Smoking deterrent study. *British Medical Journal*, 1963, 1, 486-487.

DAVISON, G. C. Appraisal of behavior modification techniques with adults in institutional settings. In C. M. Franks (Ed.), *Behavior therapy: appraisal and status*. New York: McGraw-Hill, 1969. Pp. 220-278.

DAVISON, G. C., & VALINS, S. Maintenance of self-attributed and drug-attributed behavior change. *Journal of Personality and Social Psychology*, 1969, 11, 25-33.

DORSEY, J. L. Control of the tobacco habit. *Annals of Internal Medicine*, 1936, 10, 628-631.

EDWARDS, G. Double-blind trial of lobeline in an anti-smoking clinic. *Medical Officer*, 1964, 111, 158-160.

FINNEGAN, J. K., LARSON, P. S., & HAAG, H. B. The role of nicotine in the cigarette habit. *Science*, 1945, 102, 94-96.

FORD, S., & EDERER, F. Breaking the cigarette habit. *Journal of the American Medical Association*, 1965, 194, 139-142.

GANTT, W. H. *Experimental basis for neurotic behavior*. New York: Hoeber, 1944.

GRAFF, H., HAMMET, V. O., BASH, N., FACKLER, G., YANOVSKI, A., & GOLDMAN, A. Results of four antismoking methods. *Pennsylvania Medical Journal*, 1966, 69, 86-89.

JOHNSTON, L. Tobacco smoking and nicotine. *Lancet*, 1942, 2, 742.

KAMANO, D. K. Selective review of effects of discontinuation of drug-treatment: some implications and problems. *Psychological Reports*, 1966, 19, 743-749.

KEUTZER, C. S., LICHTENSTEIN, E., & MEES, H. L. Modification of smoking behavior: a review. *Psychological Bulletin*, 1968, 70, 520-533.

LEONE, L. A., MUSIKER, H. R., ALBALA, M. M., & MCGURK, W. A study of the effectiveness of the smoking deterrence clinic. *Rhode Island Medical Journal*, 1968, 51, 247-257.

LONDON, S. J. Clinical evaluation of a new lobeline smoking deterrent. *Current Therapeutic Research*, 1963, 5, 167-175.

LUCCHESI, B. R , SCHUSTER, C. R., & EMLEY, G. S. The role of nicotine as a determinant of cigarette smoking frequency in man with observations of certain cardiovascular effects associated with the tobacco alkaloid. *Clinical Pharmacology and Therapeutics*, 1967, 8, 789-796.

MERRY, J., & PRESTON, G. The effect of buffered lobeline sulfate on cigarette smoking. *Practitioner*, 1963, 190, 629-631.

MILLER, N. E. Some animal experiments pertinent to the problem of combining psychotherapy with drug therapy. *Comprehensive Psychiatry*, 1966, 7, 1-12.

MILLER, R. E., MURPHY, J. V., & MIRSKY, I. A. Persistent effect of chlorpromazine on extinction of an avoidance response. *Archives of Neurology and Psychiatry*, 1957, 78, 526-530.

NELSON, F. Effects of chlorpromazine on fear extinction. *Journal of Comparative and Physiological Psychology*, 1967, 64, 496-498.

OVERTON, D. A. State-dependent or "dissociated" learning produced with pentobarbital. *Journal of Comparative and Physiological Psychology*, 1964, 57, 3-12.

RAPP, G. W., DUSZA, B. T., & BLANCHET, L. Absorption and utility of lobeline as a smoking deterrent. *American Journal of Medical Science*, 1959, 237, 287-292.

RAPP, G. W., & OLEN, A. A. A critical evaluation of a lobeline based smoking deterrent. *American Journal of Medical Science*, 1955, 230, 9-14.

ROSNICK, M. J. The smoking deterrent effect of a new lobeline dosage form. *Journal of the Florida Medical Association*, 1965, 52, 27-30.

SCOTT, G. W., COX, A. G. C., MACLEAN, K. S., PRICE, T. M. L., & SOUTHWELL, N. Buffered lobeline as a smoking deterrent. *Lancet*, 1962, 1, 54-55.

WRIGHT, I. S., & LITTAUER, D. Lobeline sulfate: its pharmacology and use in the treatment of the tobacco habit. *Journal of the American Medical Association*, 1937, 9, 649-654.

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