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From: W. L. Dunn

Subject: Plans and Objectives - 1980

CONFIDENTIAL

In our 1979 Plans and Objectives report we stated that there were three somewhat independent lines of investigation underway. These were:

1. The Comparative Psychology Program - Studies of the effects of nicotine and nicotine-like compounds upon animal behavior.
2. The Electroencephalography Program - Studies of the effects of smoke and smoke constituents upon the electrical activity of the human brain.
3. The Experimental Psychology Program - Studies of the effects of changes in smoke composition upon puffing behavior, inhalation behavior and the judgmental statements of smokers reacting to those changes.

These three programs are being continued through 1980.

We are adding a fourth area of investigation this year:

4. The Social Psychology Program - Studies of cigarette smoking as a psychosocial phenomenon. Sandra Dunn, Ph.D., Research Psychologist, will be be responsible for this new program.

Our aim in this new program will be to contribute to the understanding of how cigarette smoking and the social process influence one another. We will be interested, for example, in how social change effects changes in the behavior, attitudes and self-perception of the smoker, and how, conversely, cigarette smoking can have psychosocial consequences through its manifest involvement in the social situation, and also through its central-nervous-system-mediated effects upon the coping abilities of the smoking social participant.

Details of the three original lines of investigation follow. It is premature to set down concrete plans for the social psychology program. Our initial efforts in 1980 will be to formulate those plans.

I. THE COMPARATIVE PSYCHOLOGY PROGRAM...Levy Replacement, Carron and Allen

The two major objectives of the comparative psychology program are 1) to develop and use animal behavior tests to screen nicotine analogues and 2) to learn more about the reinforcing properties of nicotine. Studies designed to meet these objectives are described below.

Nicotine Discrimination

In this test rats are trained to discriminate nicotine injections from saline injections based upon the CNS effects of the injections. We have been using this test to screen nicotine analogues and plan to continue doing so during 1980 because it has proven to be an extremely sensitive and reliable test.

Tail Flick

Nicotine has analgesic properties as measured by the tail flick test (Sahley and Berntson, 1977). We have done extensive testing of (-)- and (+)-nicotine using this test. Unfortunately the data were highly variable due to the rats' severe agitation after the nicotine injections. During 1980 we plan to administer nicotine and nicotine analogues intraventricularly in an effort to obtain more reliable data.

Prostration Syndrome

A prostration syndrome in rats has been described by Abood and his coworkers (1978). This response is elicited by rapid intraventricular administration of 2-10 µg of nicotine. We have begun to routinely administer nicotine and nicotine analogues intraventricularly and to rate the resultant prostration. During 1980 we plan to continue using this test to screen analogues. In addiiton we plan to begin video taping the test sessions, and (in collaboration with F. Gullotta) record from the dorsal hippocampus during testing.

Place Preference

Mucha and Van der Kooy (1979) have reported that a place preference paradigm may be used to demonstrate the rewarding properties of morphine. We plan to use a similar paradigm to examine the rewarding effects of nicotine. Rats will be given nicotine injections in one distinctive environment and saline injections in another distinctive environment for several days. Following this training procedure, the rats will be given a choice between the two environments, and the time they spend in each will be the dependent variable. If the rats spend more time in the environment paired with the nicotine injections, this will suggest that the nicotine was reinforcing to them.

Nicotine Self-Administration

If the reinforcing properties of nicotine cannot be readily demonstrated using the place preference paradigm described above, we will try to get rats to self-administer nicotine through indwelling intravenous catheters using a procedure similar to that of Hanson and his coworkers (1977). If we are successful in getting rats to self-inject nicotine, we plan to determine a) if this behavior can be blocked by cholinergic antagonists, b) if it is dose-responsive and c) if it extinguishes when saline is substituted for nicotine.

II. ELECTROPHYSIOLOGICAL PROGRAM...Gullotta and Frankovitch

We hypothesize for this program that the smoking act is perpetuated by the salutory effect of smoke inhalation upon certain discrete as yet unspecified neural functions. We take as a premise that the effect will be present and observable in the EEG correlates of these neural functions. Our objectives in all of the following proposed studies therefore are to determine 1) if the effect is discernible in any of the various monitorable EEG patterns and if so 2) whether further knowledge of the nature of the effect can be inferred from its EEG manifestation.

Auditory Evoked Potentials and Cigarette Smoking

This study was begun in late 1979 and should be completed during the first quarter of 1980. It was initiated by reports in the literature which suggest that both nicotine administration and cigarette smoking may influence auditory evoked responses.

In a study using cats as subjects (Guha & Pradhan, 1976) it was found that low doses of nicotine enhanced auditory EPs, while high doses depressed them. In a study using humans as subjects (Friedman, et al., 1974) it was found that cigarette smoking tended to depress auditory EPs. It is extremely important to further investigate the effects of cigarette smoking on auditory EPs. If cigarette smoking does, in fact, depress auditory EPs, this would imply that nicotine has selective effects on the CNS (recall that several reports have indicated that cigarette smoking enhances visual EPs).

Cigarette Smoking and the Standard Electroencephalogram

Numerous studies have shown that both cigarette smoking and smoke deprivation affect the EEG. Cigarette smoking results in EEG changes associated with arousal, while smoke deprivation reuslts in the high amplitude, low frequency waves associated with drowsiness.

The EEG studies that have been reported thus far generally fail on one or two accounts. First, most studies have only examined EEG changes occuring over very few cortical areas. Second, the majority of these studies have used rather crude data analysis techniques.

As part of our ongoing program, we have placed electrodes over central, posterior and temporal brain areas and have recorded ongoing EEG activity. We are now in the process of developing a spectral analysis program, which will allow us to perform power spectral density analyses of ongoing EEG data from a number of brain loci under varying conditions of smoking and smoke deprivation.

Central Gating and Cigarette Smoking

Cigarette smoking appears to have opposite effects on visual and auditory evoked potentials. While visual EPs are enhanced by smoking, auditory EPs appear to be depressed. First, nicotine, rather than being a general stimulant, may be exerting a selective influence on brain structures. Second, perhaps nicotine somehow participates in the gating of information by the brain. This gating phenomenon was eloquently demonstrated in 1959 by Hernandez-Péon and has been often replicated. It could be that visual EPs are enhanced at the expense of auditory EPs.

It is possible that cigarette smoking (via nicotine) allows for selective attention in the visual mode by damping input from other sensory modes. We propose to investigate this possible relationship by using cross-modal evoked potentials. Visual and auditory EPs will be recorded in the same experiment, while attention is varied by instructional set.

Cigarette Smoking and Learning by the Brain

A number of studies have shown that cigarette smoking may facilitate certain types of learning. The mechanisms by which this facilitation is accomplished remain to be clarified. The following study may shed light on this problem.

When a dim flash of light is presented to a subject, an evoked response is recorded over specific visual projection areas. No responses are recorded from the auditory cortex. If, however, the dim flash of light is repeatedly paired with a tone, an evoked response to the flash alone will gradually develop at the auditory cortex. This type of learning is called classical conditioning and it is the fundamental building block of many "higher" forms of learning.

We propose to study the effects of cigarette smoking on the rate at which an EP develops at the auditory cortex to light flash. If smoking accelerates the rate at which conditioning occurs, these data would help explain why smoking facilitates certain types of learning.

Cigarette Smoking and Somatosensory Evoked Potentials

We have two reasons for wanting to investigate the effects of cigarette smoking on somatosensory evoked potentials. First, we wish to find out whether smoking influences this response. No literature currently exists on this topic. Any data gathered would increase our understanding of how

cigarette smoking influences brain systems mediating behavior. Second, and more importantly, we wish to investigate the proposed analgesic properties of nicotine.

Animal studies from our laboratory (Levy) and others (Berntson) suggest that nicotine may have analgesic effects on certain types of pain. Analgesics affect somatosensory EPs in known ways. If cigarette smoking influences these EPs in a similar fashion, this would be correlative evidence for cigarette smoking possessing analgesic properties in humans.

III. THE EXPERIMENTAL PSYCHOLOGY PROGRAM...Ryan and Jones

Objective #1: To gain better understanding of the role of nicotine in smoking.

First Approach: To further evaluate the smoker's ability to detect nicotine differences among cigarettes.

The first phase of this research was conducted in 1979, when we found that 9 of 10 smokers could detect nicotine differences (at 6 mg tar levels) if nicotine deliveries differed by 50%. In the second phase of this research we will extend the investigation to cigarettes at the 12 and 17 mg tar levels. These cigarettes have been ordered and should be made in January. We are looking into the possibility of a third phase, in which nicotine detectability is examined at near zero tar levels.

Second Approach: Examine smoker preference for nicotine delivery in very low tar cigarettes.

The first phase of this project consists of having consumers rate the strength and acceptability of 6 mg tar cigarettes with detectably different nicotine contents above and below the levels found in normal 6 mg models. Should it be possible to make ultra low tar models with markedly different nicotine deliveries (see above) then a second phase investigation will examine acceptability and strength ratings for cigarettes with detectably different nicotine deliveries at near zero tar. (We understand that M.A.H. Russell is engaged in similar research in England.)

Third Approach: Examine the changes in body nicotine content pre and post smoking.

Our theorizing on the role of nicotine suggests that cigarettes will be smoked whenever body nicotine content drops below a certain (unknown) level. We can detect nicotine's presence in saliva, where its concentration probably reflects its concentration in blood and tissues.

We are engaged in systematic investigation of the changes in salivary nicotine content as a function of time since smoking and magnitude of intake. Our first goal is to find the growth and decay curve of salivary nicotine concentrations after different amounts of smoking. As a second step, we will relate the salivary concentrations to the concentration of nicotine in the blood. We have had preliminary discussion of the latter problem with Dr. Arthur Ryan, in our Medical Department, and, depending on our ability to identify the salivary growth and decay data, will make a series of blood and saliva concentration measures later in the year. The exact procedure is as yet undecided, but the data will be gathered from a few volunteer subjects under medical supervision.

Assuming that salivary nicotine concentrations will reflect blood nicotine concentrations, we can then proceed to a fourth stage in the research, relating the easily obtained salivary concentrations to the urge to smoke.

Fourth Approach: Identification of two smoking population subgroups, one of which has greater nicotine needs than the other.

We have described these people in the past as compensators and non-compensators, and attempted to define them by their consumption changes when nicotine deliveries were moderately shifted. However, we've had no great success in the identification to date. Now we may have two extra tools to use: commercial PM cigarettes of ultra low tar and nicotine, and salivary nicotine concentrations. Others, principally at Columbia University, have suggested that shifts to ultra low nicotine cigarettes produce the same type of psychological stress behaviors as quitting. We therefore propose a shift study in which smokers are shifted to an ultra low brand, and the key dependent variable becomes the presence or absence of the withdrawal syndrome. Those who show evidence of nicotine dependence and those who do not can then be used to test our hypotheses on the relationship of salivary concentration to smoking behavior.

Objective #2: To better understand the mechanisms controlling cigarette acceptability.

First Approach: We will continue the Annual Monitoring of Cigarette Acceptability for a fourth year. This will exhaust our supply of available cigarettes at 5, 9, 13, 17, and 21 mg tar. It would seem reasonable to change this project slightly in 1981 by adding a 1 mg tar cigarette and dropping the 21 mg model when the next batch of cigarettes is made.

Second Approach: We have noted that some cigarettes produce a greater saliva flow than other cigarettes. This may in part be attributed to the role of nicotine and in part to RTD but it appears also in part