Pain Elicited Aggression as a Function of Withdrawal from Morphine Addiction

Teel
PAIN ELICITED AGGRESSION AS A FUNCTION OF WITHDRAWAL FROM MORPHINE ADDICTION

by

Brian G. Teel

A Thesis submitted to the Faculty of the School of Graduate Studies in partial fulfillment of the Degree of Master of Arts

Western Michigan University
Kalamazoo, Michigan
December, 1966
ACKNOWLEDGMENTS

The investigator wishes to express his sincere appreciation to the many persons who have offered their assistance in obtaining materials and providing advice for the production of this thesis.

Special mention is due to Dr. John Nangle, Dr. Paul Mountjoy and Dr. Christopher Koronakos for their comments regarding this paper and especially to Dr. Donald H. Thor for his valuable assistance from the beginning of this enterprise.

Brian G. Teel
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>THE OBJECTIVES OF PRESENT RESEARCH</td>
<td>1</td>
</tr>
<tr>
<td>The Objectives of this Study</td>
<td>4</td>
</tr>
<tr>
<td>THE METHOD OF STUDY</td>
<td>5</td>
</tr>
<tr>
<td>The Subjects</td>
<td>5</td>
</tr>
<tr>
<td>The Apparatus</td>
<td>6</td>
</tr>
<tr>
<td>The Procedure</td>
<td>7</td>
</tr>
<tr>
<td>THE RESULTS OF THIS STUDY</td>
<td>9</td>
</tr>
<tr>
<td>THE DISCUSSION OF THE RESULTS</td>
<td>11</td>
</tr>
<tr>
<td>THE SUMMARY</td>
<td>14</td>
</tr>
<tr>
<td>FIGURE 1</td>
<td>15</td>
</tr>
<tr>
<td>FIGURE 2</td>
<td>16</td>
</tr>
<tr>
<td>TABLE 1</td>
<td>17</td>
</tr>
<tr>
<td>THE REFERENCES</td>
<td>18</td>
</tr>
</tbody>
</table>
One branch of aggression research has concentrated on the elicitation of aggressive behavior by means of exteroceptive stimulation. Electric shock or similar painful stimuli (Ulrich & Azrin, 1962) are well known to produce fighting in the laboratory rat. This basic method has allowed experimental analysis of a wide scope of associated variables.

Ulrich and Azrin (1962) investigated several different parameters. They found that laboratory rats increased their fighting behavior as the frequency of shocks increased from 0.1 to 38 shocks per minute. With frequency fixed, the fighting response rate resembled an inverted U-shaped curve when shock intensity was increased from low 0.5 milliamperes, to optimal 2.0 ma, to high 5.0 ma. When the aversive stimulus was continued for an extended period of time the fighting response was extremely resistant to reflex fatigue. During the first hour fighting was elicited on 82% of the shocks. After six hours and nearly 15,000 shocks the response rate dropped below 40% for the next 1.5 hours and the Ss appeared to be weakened physically. Using a fixed frequency and intensity, the authors varied the size of the enclosure. When the Ss were confined in a very small area, 0.25 square feet, the fighting response was elicited by 90% of the shocks. After the floor area was increased to 2.25 square feet the response rate dropped to only 2%
Azrin, Ulrich, Hutchinson, and Norman (1964) found that fighting was a direct function of the duration of the shock stimulus. They varied the shock duration from 0.075 to 3.0 sec. delivered every three seconds. Shock durations above 0.5 sec. elicited fighting responses from 90% to 97% of the time for the first 20 shocks. This rate was only 25% when shock duration was 0.075 sec. However, a total of 200 shocks was delivered at each duration level during each of the 12 experimental sessions. Analysis of within session variability indicated that the long duration shocks lost their effectiveness as each session continued while the short duration shocks became more effective. During the last third of each session the short shock durations averaged a higher response ratio than the long durations.

Hutchinson, Ulrich and Azrin (1965) investigated the effects of age, isolation, castration, and prior experience with pain-elicited aggression. A monotonic relationship was found between age and aggression with eight groups of rats from 24 to 93 days of age when each group was given 100 shocks. Rats raised in isolation proved to be less aggressive than Ss raised in community conditions. Isolated 90 day old Ss fought after 48% of the shocks as opposed to a rate of 85% for nonisolated Ss of the same age. Castration was found to decrease aggression in adult rats when performed either pre- or post-puberty. Finally, the authors found that the rate of aggressive responses depended upon the prior history of aggressive behavior. The Ss were kept in
isolation except for daily trials from the time they were 21 days old until they were 100 days old. They exhibited a higher rate of response at any given age than did any other groups isolated or nonisolated, who had no prior experience.

Flory, Ulrich and Wolff (1965) used the exteroceptive aversive stimulus method to investigate effects of visual impairment. They found that rats with permanent visual impairment; i.e., the surgical removal of their eyes, emitted significantly fewer responses than rats with normal vision, but more responses than temporarily impaired Ss who wore hoods over their eyes. However, when tactile stimulation was eliminated from the permanently impaired Ss by vibrissae removal the combined effect equaled the effect of the hoods. Apparently, the hoods had restricted the use of the vibrissae as providers of tactile stimulation.

However, it may be noted that human aggression frequently does not involve easily distinguished overt aversive stimulation. Often, aversive stimulation cannot be identified and hence must be inferred; e.g., as in the aggressive behavior of a husband home from a bad day at the office. This stimulation frequently is referred to as being psychologically disturbing or painful (Ulrich, 1965).

Furthermore, there are numerous instances where aversive stimulation obviously is interoceptive (headache, gastric distress, tumors, etc.). Examples of this type of stimulation include that stimulation caused by withdrawal from drug and alcoholic states.
It is more reasonable to infer covert stimulation resulting in aggressive behavior in these instances, since it is well known that distinct physiological changes are caused by these chemical agents. The experimental analysis of aggression caused by stimulation other than exteroceptive stimulation logically may begin with the investigation of one of these states. This study was designed to demonstrate that aggressive behavior can be a function of such internal stimulation.

While investigating another topic, Boshka, Weisman and Thor (1966) noted that rats engaged in aggressive behavior for a period of 36 hours when placed in a group cage 48 hours after their last injection of morphine sulfate. Unfortunately, no record of the frequency of aggressive responses was made, since this was not the purpose of the study. The present study was designed to quantify the frequency of aggressive behavior at various levels of drug intake in order to demonstrate that aggressive behavior is not simply a function of the injection of the drug, but also is a function of the amount of the drug used and the interval of time from the last injection.
Subjects

Thirty male Sprague-Dawley rats of the Holtzman strain were used as Ss. This strain is noted for its docility and nonaggressive behavior (Ulrich & Azrin, 1962). The Ss were 78 days old at the beginning of the experiment and had an average mass of 298 g. None of the Ss had prior experience with any type of experimental procedure.

The Ss were randomly assigned to one of two control and three experimental groups. From the beginning of the experiment they were kept in separate cages until after their last injection at which time all of the Ss in each group were placed in one large cage. All of the Ss were maintained on a free-feeding diet with food and water available at all times. Henceforth the Ss will be referred to as the experimental groups E1, E2 or E3 or as the control groups C1 or C2.
Apparatus

The analgesic drug morphine sulfate was used to establish the internal state leading to interoceptive aversive stimulation. This was chosen because of the relative ease of administering this drug to laboratory animals.

The group cages measured 16 in. by 11.5 in. by 7.5 in. A hand counter was used to register the number of aggressive responses. Morphine sulfate was administered intraperitoneally with a standard 1 cc. syringe and a 1/4 in. 27 G needle. Dilute concentrations were given using a commercially prepared solution (Lilly, HT, No. 16) and more concentrated solutions were prepared by use of morphine sulfate hypodermic tablets (Lilly, HT, No. 134) in sterile distilled water.

Although not soundproof, the small experimental room was very quiet because it was isolated from areas of normal activity. Overhead fluorescent lighting provided a constant light source. The light was interrupted for one experimental group due to a six hour long power failure occurring from 8 a.m. to 2 p.m on the fourth day of observation of group E2.
Procedure

The three experimental groups began a program of injections proceeding from an initial dosage of 5 mg. of morphine sulfate per kg. body weight, administered intraperitoneally every six hours (20 mg./kg. per day), to a final dosage level of 100 mg./kg. per day for E1, 200 mg./kg. per day for E2 and 400 mg./kg. per day for E3. Each group was maintained at its respective maximal level for three days prior to the termination of injections. The dosages were increased by 5 mg./kg. per injection each successive day; after E3 reached the rate of 200 mg./kg. per day, the new rates were 10% greater than those of the preceding day. There appeared to be no problems with this injection schedule, since all the Ss tolerated the injection program well.

The two control groups were handled in a similar fashion. C1 was picked up and handled for approximately the same amount of time and in the same manner as the experimental Ss. C2 was given an intraperitoneal injection of sterile distilled water each time the experimental groups were injected.

The length of the injection period varied with the group; seven days for E1, 12 days for E2 and C1 and 22 days for E3 and C2. Each group received its last injection at 1 p.m. and placed immediately into the group cage and observed for a random sample period
of 15 minutes every two hours for six days.

An aggressive response was defined as the act of two Ss facing each other in an upright, sterotyped posture, "with the head thrust forward and the mouth open", during which time the Ss would alternately strike at and draw back from each other (Ulrich & Azrin, 1962, p. 512). Only one response was scored although both Ss typically struck at each other simultaneously.
RESULTS

Figure 1 shows a cumulative record of the responses of the five groups. C1 made only two responses during the entire observation period.

C2 and E1 demonstrated the greatest similarity in regard to total responses (E1 was responding at a rate 20% greater than C2 for the entire period); however, the topography of the response curves differed greatly (Fig. 1 and Table 1). Ss in C2 had completed 78% of their responses by the time E1 responded once, and all of the C2 responses were recorded prior to the beginning of uninterrupted responding by all of the experimental groups.

E1 demonstrated a mild response rate, the least of all the experimental groups. E2 demonstrated an increase of 48% over the response rate of E1. As noted earlier, a power failure occurred from 92-98 hours into the experiment resulting in a period of darkness for group E2. During this six hour period the E2 group slept during all observational periods. However, it was during this period that the other two experimental groups emitted 22% of their total responses. (A similar response rate by E2 would have added 20 additional responses.)

E3 presented a 526% increase in responses over E2. The response curve demonstrates a rapid rise to a high rate and an
abrupt decline during the last 12 hours of responding. The Ss in all three experimental groups began and stopped responding at almost identical times. Nichols (1963, pp. 895-904) noted that "the withdrawal syndrome seems to reach a peak of distress about two to four days after the last morphine intake." In the same paper he stated that "the peak of withdrawal distress seems to occur approximately three days after the last morphine intake." This study indicates that aggressive behavior, presumably a measure of withdrawal distress, does not peak until the fourth and fifth days after the last morphine intake for mild, moderate and severe levels of morphine intake.

As noted by Ulrich and Azrin (1962), there was no difficulty in identifying a fighting response. The Ss would squeal and face each other in the stereotyped posture, occasionally striking each other. The Ss always fought in pairs, although two or all three pairs sometimes fought simultaneously, particularly with E3. Figure 2 presents examples of this type of behavior. Typically, the Ss would remain in this posture for most of time between attacks.

The Ss made no further responses, and appeared to behave normally 122 hours after the last injection.
DISCUSSION

The data support the hypothesis that aggressive behavior may be a function of the noxious interoceptive stimulation caused by withdrawal from morphine addiction. This aggressive behavior depends upon the amount of morphine administered and the amount of time since the last intake.

Aggressive behavior is not commonly found in these docile Ss, as evidenced by C1. The behavior is not simply a matter of pain caused by too frequent injections, although C2 did respond frequently. Since sterile distilled water was used, instead of a non-irritating solution such as saline, the aggressive behavior of C2 may be attributed in part to the pain caused by the injection, per se and in part to the solution injected. Presumably, C2 stopped responding when the pain from the injections of water subsided. Since this was prior to the beginning of the responses of the experimental groups, it may be assumed that the injection and solution-irritation effects did not increase the response rate of the experimental Ss.

Although the maximal dose for E3 was twice that of E2 and E1, there was no expectation that the responses would comply with monotonic increases equal to the increases in dosage rates. In fact, E3 was given almost three times the total amount of morphine
as E2, and E2 three times as much as El. Of course, the ratio of total amounts could be equated to the ratio of maximal dosages by adjusting the total time the Ss remained on the injection schedule. It might be fruitful to investigate the relationships between daily amount, total amount and total time. This could be useful in determining possible carry-over effects.

Other parameters deserving study would include the size of the enclosure and the number of Ss per group. Aggressive behavior may depend upon close proximity or upon actual contact with other Ss. A detailed investigation may determine the necessity of contact as an additional stimulant of aggressive behavior (Ulrich & Azrin, 1962).

Since E2 made no response when the light was not on, light intensity should be varied to determine the degree to which outside stimulation increases withdrawal aggression. The same procedure could be used to determine the effects of sound frequencies and intensities.

Further extensions would involve comparisons of morphine and other drugs to determine relative withdrawal distress. This might aid in understanding the effects of new drugs and need not be limited only to addicting drugs. It may be possible to determine the irritating characteristics of a non-sedative solution by observing the degree to which the Ss fight immediately after termination of intake.
One other advantage is that methods of alleviating withdrawal distress may be objectively evaluated. Also, it should be possible to quantitatively evaluate the relative effectiveness of general pain killers not directly associated with withdrawal distress.
SUMMARY

Thirty male rats were randomly assigned to one of two control or three experimental groups. The experimental Ss were injected intraperitoneally with a solution of morphine sulfate, beginning at 20 mg./kg. day and increasing to a maximal dosage level of 100 mg./kg. day for E1, 200 mg./kg. day for E2 and 400 mg./kg. day for E3. One control group was injected intraperitoneally with sterile distilled water. The other control group was handled but not injected. When placed in a group cage immediately after the final intake the experimental Ss fought at a higher rate than did the control Ss. The degree of aggressive behavior was directly related to the amount of morphine injected. The injected control group fought at a significantly higher rate than did the control group that had been handled and continued fighting until 60 hours after the final injection. The experimental groups began responding 60 hours after the final injection and continued to 130 hours.
Fig. 1. Cumulative record of the fighting responses emitted by each group of Ss for an 130 hour period following final intake of morphine sulfate.
Fig. 2 Samples of aggressive behavior in absence of exteroceptive painful stimuli
### Table 1

Examples of the differences over time of different groups of Ss deprived of morphine sulfate.

<table>
<thead>
<tr>
<th>Hours from final injection of morphine sulfate</th>
<th>Total fighting responses per period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C1</td>
</tr>
<tr>
<td>0-11</td>
<td>-</td>
</tr>
<tr>
<td>12-23</td>
<td>1</td>
</tr>
<tr>
<td>24-35</td>
<td>-</td>
</tr>
<tr>
<td>36-47</td>
<td>-</td>
</tr>
<tr>
<td>48-59</td>
<td>1</td>
</tr>
<tr>
<td>60-71</td>
<td>-</td>
</tr>
<tr>
<td>72-83</td>
<td>-</td>
</tr>
<tr>
<td>84-95</td>
<td>-</td>
</tr>
<tr>
<td>96-107</td>
<td>-</td>
</tr>
<tr>
<td>108-119</td>
<td>-</td>
</tr>
<tr>
<td>120-131</td>
<td>-</td>
</tr>
</tbody>
</table>

*Note-These periods included a six hour period of power failure during which the Ss in E2 emitted no responses.
References


