EXPERIMENTAL CINGULUMOTOMY AND MODIFICATION OF MORPHINE WITHDRAWAL*

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Withdrawal of morphine from the addicted individual has been a clinical problem for many years. The neurological problems in addiction and withdrawal are poorly understood and laboratory investigations have been few.16,29,30,36,41 The manner in which the nervous system becomes dependent upon this drug and the precise fashion in which the function of the nervous system is deranged in the withdrawal syndrome remain unknown. Several clinical techniques have been used to reduce or obscure the effects of withdrawal, such as severe insulin-induced hypoglycemia,3 metrazol-induced convulsions,2 electricity shock therapy,15,21 steroid therapy, and prefrontal lobotomy. Only prefrontal lobotomy, however, gives any degree of differential modification of symptoms of withdrawal that might aid in understanding the neurophysiological derangements present when the drug is withdrawn.

Modification of the syndrome of morphine withdrawal by prefrontal lobotomy has been recognized clinically since 1946.29 Even so, there has been prolonged disagreement as to whether this procedure relieves the signs and symptoms completely12,17,20,22 or simply modifies them.9,14,22,24,40 There is as yet no generally accepted basis for these effects, and explanations have varied from loss of psychic craving21 to simple obscuration of the abstinence syndrome by postoperative lethargy and loss of integrated cerebral activity as a result of extensive damage to the brain or "diaphragm."40

The lesions included in frontal lobotomy vary a great deal since varied technical procedures are used to sever the frontal fiber tracts. The resultant variability of the lesions could be the cause for the divergent opinions on the effects of frontal lobe lesions on the abstinence syndrome. A few careful pathological studies have shown this variability and likewise indicate that only two fiber tracts, the cingulate fasciculus and the uncinate fasciculus, are consistently sectioned in the usual frontal or prefrontal lobotomies.22,23

Previous experiments have shown the reliability of producing morphine

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addiction and studying effects of withdrawal of the narcotic in both dogs\textsuperscript{36,37} and monkeys.\textsuperscript{18,29,30} Thus, experimental abstinence produces signs and symptoms generally related to one of two groups—(1) The “psychic” or “purposive dependence” group, and (2) the “somatic” or “nonpurposive dependence” group.\textsuperscript{36} The former group of signs and symptoms has been related to psychic drives in which a strong volitional element on the part of the addict exists, and the latter group has been presumed secondary to effects on the autonomic system with no volitional element involved. This more or less arbitrary division might be used to study the selective effects of specific lesions of the frontal lobe on the syndrome of experimental abstinence.

The original purpose of this study was to determine what effects certain selective lesions of the frontal lobe might have on the “psychic” and “somatic” components of experimental withdrawal of morphine in monkeys. In view of observations already made, the frontal lobe lesions selected for study were frontal lobectomy,\textsuperscript{10,22,36} resection of the cingulate gyrus,\textsuperscript{18,19,22,33} and stereotaxic cingulumotomy.\textsuperscript{7} Thus, the lesions ranged from massive loss of the frontal lobe to minimal physical lesion in the cingulum. Bilateral and unilateral lesions were studied because of previous controversies.\textsuperscript{27,35,40} Control procedures were designed to rule out the effects of the operative exposure and massive removal of brain in regions other than frontal lobe.

A secondary purpose was to determine briefly if a similar chronic frontal lobe lesion could change the susceptibility to addiction or cause a persistent alteration of the abstinence syndrome.

\textbf{METHODS}

Fourteen monkeys (\textit{Macaca mulatta}), 6 males and 8 females, were used in the chronic series of experiments. All animals were immature, and weighed from 3 to 5 kg. Ten animals were addicted to morphine sulfate, and 12 operative procedures were carried out on 8 of these animals (Table 1). Of the remaining 2 addicts, 1 died in acute morphinism, and 1 died in morphine withdrawal. One animal was used for an anatomical control, 2 were used for pharmacological controls involving Nalline\textsuperscript{*} and 1 was given saline injections for a control on the production of addiction. Table 1 shows the basic outline of this series of experiments and diagrams the sequence in which each animal was used in the serially arranged schedule of procedures.

\textit{Addictions.} All animals were addicted to morphine sulfate by the method originally described by Kolb and DuMez.\textsuperscript{16} For 4 to 6 weeks, injections of morphine sulfate were given subcutaneously twice daily in increasing doses until the animal tolerated a daily dose of 135 to 200 mg. Evidences of addiction\textsuperscript{16,29} appeared as a rule on the 8th to 9th day of injections. An animal receiving morphine injections was considered to be addicted when cessation of morphine injections resulted in an unequivocal withdrawal syndrome.

All animals to be addicted were observed carefully for a period of 2 weeks

\textsuperscript{*} Kindly supplied by Merck & Co.