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Further Observations on Addiction to Methadon in the Monkey.*

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In a study previously reported, Woods, Wyngaarden, and Seevers[1] found that the monkey (*Macaca mulatta*) did not develop a significant degree of dependence to racemic methadon† if the maximum tolerated dose was administered once a day for a period of 4 months. Since these results are at variance with those obtained in the dog which shows marked signs during the first day of withdrawal,[2] and in former morphine addicts who demonstrate a delayed and atypical abstinence syndrome beginning 5 days after the last dose,[3] it becomes essential to know whether a species difference exists in response to this drug; whether previous studies on the monkey were not correctly designed to establish physical dependence because of the long interval between doses (24 hours); or whether the normal monkey responds to the drug like the normal non-addict human (no case of primary addiction to this drug having been reported thus far in this group of individuals). In view of the fact that clinical facilities for studies of addiction may be inadequate to take care of the large number of new analgesics coming to clinical trial, it is important to determine whether animals are of any value for preliminary screening of the addiction potentiality of new compounds.

To obtain further information, racemic methadon was administered to 4 monkeys thrice daily in initial dosage of 2 mg/kg and raised to 7 mg/kg within 66 days, and continued thereafter on this regimen until the termination of the experiment. Increase in the dosage above 7 mg/kg resulted in excessive depression, loss of appetite and weight, but the animals remained in excellent condition on this dose. The two morphine controls were raised from initial dosage of 5 mg/kg (15 mg/kg daily) to 50 mg/kg (150 mg/kg daily) in 112 days and continued thereafter on this dose.

After 142 days of poisoning, both drugs were withdrawn and observations were made through a one-way vision glass panel, a technical installation which eliminates modification of the animal's behavior by the presence of the observer. Abstinence signs[4] were absent or minimal after methadon was withdrawn. Very slight pilomotor activity was present in all 4 animals after 30 hours, but disappeared at the end of 72 hours. After 36 hours, the monkeys were somewhat more irritable than during the period of administration but this, we believe, is a manifestation of the elimination of the slight depression produced by the methadon and a return to normal excitability rather than a true state of hyperexcitability. No anorexia was noted. One animal showed moderate inflammation of the eyelids and cornea on the fourth day of withdrawal and two had slight diarrhea on the fourth day. Otherwise no significant changes were observed.

Very marked signs were noted in both animals withdrawn from morphine. One of these animals showed the most dramatic and severe abstinence signs ever observed by the senior author. This animal showed lacrimation, inflammation of the eyelids and cornea 20 hours after withdrawal. Shivering, facial perspiration, chattering, intention tremor, muscular rigidity, twitching, and pilomotor

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1 Woods, L. A., Wyngaarden, J. B., and Seevers, M. H., Proc. Soc. Exp. Biol. and Med., 1947, **65**, 113.

† Through the courtesy of Dr. C. A. Bratton of Parke Davis & Co.

2 Wikler, A., and Frank, K., *Fed. Proc.*, 1947, **6**, 384.

3 Isbell, H., Wikler, A., Eddy, N. B., Wilson, J. L., and Moran, C. F., *J.A.M.A.*, 1947, **135**, 888.

4 Seevers, M. H., *J. Pharm. Exp. Therap.*, 1936, **56**, 147.

activity were also noted at this time. Within a few hours the animal was lying on its side and severe dyspnea was observed. This condition became steadily worse, and no food or water was ingested. This state continued during the second and the third day, the animal becoming progressively weaker until it was unable to rise. Seventy-six hours after withdrawal, when the monkey was removed from its cage to be photographed, excitement and struggling led to further exhaustion and extreme weakness. Respiration was irregular, the animal was cyanotic, and it appeared to be moribund. Emergency measures such as intravenous glucose, injection of caffeine, etc., were attempted in an effort to save the animal, but they were without avail. Postmortem examination indicated an acutely dilated heart but no other significant changes were noted. The animal was generally in a good state of nutrition. Withdrawal signs in the other morphine animal were also severe, but not as striking as those just described.

Since these results are in essential agreement with those previously described by us,[1] it seems apparent that the normal monkey differs from the dog and from the former human morphine addict in response to this compound. The question must naturally be raised as to whether prolonged poisoning with morphine modifies or conditions the response of the human individual to subsequently administered methadon and/or other compounds and if so whether normal human subjects, previously not addicted to morphine react like the monkey or like the dog. In view of the fact that no primary case of methadon addiction has thus far been described in man, the evidence to date suggests that the response of the normal monkey is similar to that of the non-addict.

Summary. Racemic methadon administered thrice daily in maximal tolerated dose, does not induce a significant degree of physical dependence in the monkey (*Macaca mulatta*) confirming previous experiments involving single daily administration.

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Activity Curves of Crude and Purified Inhibitors and Accelerators of Blood Coagulation.*

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Most crude extracts of tissues possess in a variable proportion, clot inhibiting as well as clot accelerating substances.[1] Ordinarily, the clot accelerators are in dominance, and their action tends to mask the presence of the inhibitors. It seems from the evidence here presented that testing the activity of these extracts or their purified derivatives at different concentrations makes it possible to tell if they consist of such mixtures and, if so, whether they are *predominantly* clot accelerators or clot inhibitors. Moreover, the relative degree of purity (*i.e.* freedom from the antagonist) of the extracts is reflected by the character of their own activity curves. An extension of this concept has been made to the examination of the coagulant and anticoagulant content of other complex mixtures such as blood, plasma, and plasma fractions.

1. Activity of crude cephalin mixtures. Cephalin was prepared from acetone dried human brain by a method previously described.[2] *Crude cephalin* refers to the prod-

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1 Tocantins, L. M., Carroll, R. T., and McBride, T. J., PROC. SOC. EXP. BIOL. AND MED., 1948, **68**, 110.

2 Tocantins, L. M., *Am. J. Physiol.*, 1945, **143**, 67.