

17071. Influence of Chronic Morphine Poisoning on Growth and Metabolism of the Albino Rat.*

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The appearance of signs of hyperirritability following withdrawal of morphine in certain animal species which have received the drug for a prolonged period of time is fairly well established. Plant and Slaughter¹ and Barbour, Porter and Seelye² have presented evidence which might suggest that in the dog these phenomena are related to an increased basal metabolic rate. In line with a conception relating withdrawal signs to an elevated metabolism of tissues is the observation by Shideman and Seevers³ that skeletal muscle obtained from rats chronically poisoned with morphine exhibits an increased oxygen consumption which attains a maximum value 48 hours following withdrawal of the drug. At this time oxygen uptake is approximately twice that of muscle obtained from normal animals. The presence of such a marked increase in the metabolism of skeletal muscle *in vitro* should be reflected in an elevated basal metabolic rate of the animal during the withdrawal period. On the other hand, the presence of certain factors existing *in vivo* (neural and humoral) might mask this increased activity which would become apparent only when relieved of these factors. Swann⁴ stated that, during addiction in the rat, morphine has a specific dynamic action on metabolism but that withdrawal is followed by a violent depression of the B.M.R. In order to obtain more information on the

metabolic effects of addiction to morphine and its withdrawal in the rat, the following experiments were performed.

Experimental. Two groups of albino rats (12 in each group), averaging approximately 100 g in weight were placed on a diet of ground Purina chow for a period of 9 days. During this period individual food intake, and weight change were determined. The B.M.R. for each animal was obtained by measuring respiratory exchange over two 30 minute periods in a closed system maintained at 29°C in a constant temperature water bath. Air, to which oxygen was added as required, was continually circulated through the system. Oxygen consumption was measured by means of a small spirometer and carbon dioxide was absorbed in alkali which was analyzed for carbonate before and after each experimental period. Surface area for each animal was calculated by the formula of Diack.⁵

Following this control period one group of animals was chronically poisoned with morphine as described previously.⁶ When the dose of morphine had reached 200 mg/kg (over a period of 8 weeks) and been maintained at that level for at least a week the drug was discontinued and the B.M.R. again determined on each rat in this group as well as in the control groups. During the fourth week of the experiment, one of the animals receiving morphine died and any previous results obtained on that animal were not used in determining means and in statistical analysis.

Results. At the beginning of the experiment the mean weight of each group of animals was approximately the same (Fig.1). During the control period, prior to the administration of morphine, the average gain in

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¹ Plant, O. H., and Slaughter, D. H., *J. Pharm. and Exp. Therap.*, 1936, **58**, 417.

² Barbour, H. G., Porter, J. A., and Seelye, J. M., *J. Pharm. and Exp. Therap.*, 1939, **65**, 332.

³ Shideman, F. E., and Seevers, M. H., *J. Pharm. and Exp. Therap.*, 1942, **74**, 88.

⁴ Swann, H. G., *Am. J. Physiol.*, 1941, **133**, 467.

⁵ Diack, S. L., *J. Nutrition*, 1930-31, **3**, 289.

⁶ Shideman, F. E., and Seevers, M. H., *J. Pharm. and Exp. Therap.*, 1941, **71**, 383.

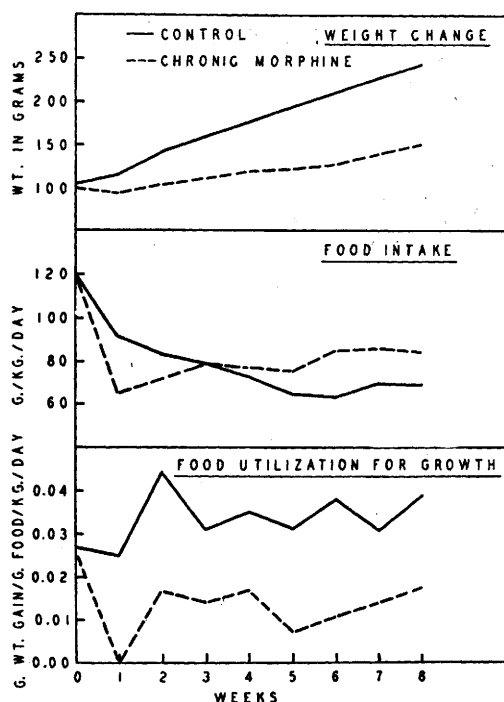


FIG. 1.

The effect of chronic morphine poisoning on the growth, food intake, and food utilization of the albino rat.

weight, food intake in g/kg and grams of weight gain per gram of food consumed per kilo of body weight per day were about equal in the two groups. (Fig. 1). This latter figure gives some indication of the utilization of food for synthesis of body tissues. During the period of the experiment, the rats receiving morphine showed a slight loss in weight during the first week followed by a gradual increase during the ensuing seven weeks. The rate of growth was much slower than in the control group. This great difference in rate of weight gain is out of proportion to the difference in food intake in the two groups (Fig. 1). The food intake of the group of animals receiving morphine is somewhat less than that of the other group of animals during the first 2 weeks but after this time is equal to, or greater than that of the control animals. The normal animals consistently utilized much more food for growth than did the animals receiving morphine. This is shown by the values obtained for grams of weight

gain per day per gram of food consumed per kilogram of body weight.

Before administration of morphine was begun in the one group of rats, the mean basal metabolic rates in the two groups were approximately the same (Table I) and there was no statistically significant difference between the 2 (t of dif. = 0.664). At the end of 8 weeks the values in both groups dropped significantly. However, the fall in the mean B.M.R. of the chronically morphinized rats at the 48 hour withdrawal period was only 47.50% as great as that obtained in the control group and was significantly higher (t of dif. = 3.824) than that of the normal animals at that time. It will also be noted that whereas the mean R.Q. of the normal rats decreased slightly over the 8 weeks period, that of the chronically morphinized rats fell more markedly and significantly (t of dif. = 3.41).

Discussion. There is little information in the literature in regard to the effects of chronic morphine poisoning and withdrawal of the drug on weight change, food utilization and metabolic rate of the rat. Myers and Flynn⁷ administered 1 to 5 mg/kg/day to young growing rats over a period of 55 days, with only a slight impairment of growth. If higher doses had been given, it is probable more pronounced effects might have been obtained. Sollmann⁸ had previously reported that feeding morphine in the diet in doses increasing from 0.01 to 35 mg/kg/day over a period of 21 weeks increased the rate of growth of young rats during the first 15 weeks. The significance of such results is questionable since there were only two animals in the experimental group. Hildebrandt⁹ poisoned rats with morphine, beginning with a dose of 100 mg/kg/day and increasing rapidly to 600 to 1000 mg/kg/day. After two weeks his experimental animals showed a marked weight loss. It is surprising, in view of the fact that he

⁷ Myers, H. B., and Flynn, J. B., *PROC. SOC. EXP. BIOL. AND MED.*, 1928, **25**, 786.

⁸ Sollmann, T., *J. Pharm. and Exp. Therap.*, 1924, **23**, 449.

⁹ Hildebrandt, F., *Arch. Exp. Path. Pharmacol.*, 1932, **92**, 68.

TABLE I.
Effect of Withdrawal Following Chronic Morphine Poisoning on the Respiratory Quotient and Metabolic Rate of the Rat.

	No. of animals	Initial		Final	
		BMR	R.Q.	BMR	R.Q.
Normal	12	51.5 (<i>t</i> = 55.6)	.829 (<i>t</i> = 53.9)	41.95 (<i>t</i> = 29.4)	.812 (<i>t</i> = 36.2)
Chronic Morphine	11	53.3 (<i>t</i> = 29.2)	.830 (<i>t</i> = 48.08)	48.86* (<i>t</i> = 44.1)	.764* (<i>t</i> = 94.8)

* Values obtained 48 hours after withdrawal of the drug which had been administered in increasing doses (from 20 mg/kg/day to 200 mg/kg/day) over a period of 8 weeks.

was using larger doses and younger rats than were employed in these experiments, that the inhibition of growth was not noted sooner.

It is difficult to interpret the changes in basal metabolic rate of the two groups of animals in the experiments reported here. If the final values were the only ones available to compare, it could be concluded that during the withdrawal period there was an increase in metabolism. However, in view of the fact that the metabolic rate of both groups decreased and since the decrease in each is roughly proportional to the gain in weight, it is possible the final difference is merely due to a difference in weight between the two groups. Nevertheless, the lower respiratory quotient and decreased utilization of food for body growth might indicate an increase in

metabolic rate which is not apparent from the values obtained for basal metabolic rates. Further experiments are planned to clarify the questions provoked by these results.

Summary. Chronic administration of morphine in doses increasing from 20 mg/kg/day to 200 mg/kg/day over a period of 8 weeks to young albino rats resulted in a marked suppression of growth. This occurred in spite of a greater food intake per unit of body weight. In addition, the animals receiving morphine demonstrated a significant reduction in their respiratory quotients at the 48 hour withdrawal period. The interpretation of the changes in metabolic rate is not apparent on the basis of the results obtained.

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17072. Value of Calcium Hypophosphite and Other Calcium Compounds as Calcium Supplements in Calcium-Low Diets.

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The value of hypophosphites as therapeutic agents has never been objectively demonstrated and Marriott's criticism of their use¹ has largely been accepted. However, calcium hypophosphite is well worth while being considered as a means of convenient calcium administration, where such therapy is desired, because it is high in this element (23%), does not have the objectionable taste of most

calcium salts and, in contrast to gluconate, is adequately soluble. The hypophosphite ion, as a stable acid, balances the alkalinity of the calcium, which effect persists even if there should occur a transformation into phosphoric acid. Therefore, the salt does not shift the acid-base equilibrium to the alkaline side as is the case with salts of carbonate producing acids. The original purpose of the present investigation was a comparison of calcium hypophosphite with dicalcium phosphate and calcium gluconate as a supplement in a cal-

¹ Marriott, McKim, *J. Am. Med. Assn.*, 1916, **76**, 486.