

septum be excluded, reveals that in no case is this interval greater than 5 sigma, which is within the limit of the error of measurement. (2) The right ventricular surface receives its excitation only 5 sigma earlier than that of the left, the error of measurement having been taken into account. This time-difference is measured in sigma, not in hundredths of a second as were those of Lewis and Rothschild. (3) In over 80% of the cases, the epicardial surface overlying the interventricular septum apparently receives its excitation very definitely ahead of the remaining right and left myocardial surfaces, in some instances to the extent of 17.5 sigma.

The results now reported suggest that the impulses spread more rapidly than generally stated through the myocardial tissue so as to reach all points of the anterior and posterior surfaces practically simultaneously. A more thorough reinvestigation of the velocity as well as the spread of the cardiac impulses seems to be indicated.

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A Rat Test for Drug Addiction.*

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Further experiments on the addiction liability of various drugs in the albino rat have been carried out by the method previously described.¹ The test measures objectively progressive changes in the degree of irritability of the animal 24 hours after withdrawal of the drug throughout the period of administration. Advantage is thus taken of the most outstanding part of the abstinence syndrome clinically and experimentally, hyperirritability, to assess the ability of a drug to produce addiction.

The irritability of the rat which is normally fairly constant for a series of animals is quantitatively measured by determining the struggle response to a uniformly uncomfortable situation. Such a situation is provided by lashing the animal in the supine position to a small animal board so constructed that the animal is free to

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¹ Himmelsbach, Gerlach, Stanton, *J. Pharm. Exp. Therap.*, 1935, **53**, 179.

struggle but can neither injure nor extricate itself. Graphic records of each struggle are made kymographically by a light lever attached to the skin overlying the xyphoid process. The response of the animal is expressed by the number of struggles per interval and is a quantitative index of the degree of irritability of the animal at that time.

Daily administration of morphine, codeine, or heroine results consistently in progressive increase of 24-hour abstinence hyperirritability as shown by the struggle response to the above described uniformly uncomfortable situation.¹ Control animals receiving injections of water showed only a gradual decrease in irritability under the same experimental conditions.

Dihydromorphinone hydrochloride (dilaudid): To completely eliminate the movements of rats in the device described above, dilaudid was 10 times as potent as morphine. Complete tranquilization was obtained with dilaudid in one-tenth of the dosage necessary with morphine. When daily doses of equal tranquilizing potency were given, no significant difference in addiction liability could be found between dilaudid and morphine. Tolerance, judged by response to the same uncomfortable situation, one hour after injection, developed to the same degree in daily administration of both morphine and dilaudid. Likewise, no difference in the duration of hyperirritability upon the abrupt and complete withdrawal of the drugs was found.

Barbiturates: Two barbiturates were administered subcutaneously daily for a period of 7 weeks. Pentobarbital-sodium, a short-acting member of this series, was given in 30, 15, and 5% M.F.D. daily while phenobarbital-sodium, a long-acting barbiturate with marked cumulative action, was administered at 15 and 5% M.F.D. daily. No increase in abstinence irritability to either drug was found. On the contrary, irritability decreased progressively below the control level indicating some cumulation of depressive effect of both drugs. Only a minor degree of tolerance to the maximal effects was indicated by the struggle response of the rats one hour after injection but the duration of somnifacient action of pentobarbital appeared by direct observation to be markedly shortened at the end of the experimental period.

Acetanilid: Clinical reports of acetanilid addiction as well as the report of Payne² of the production of abstinence symptoms in dogs suggested its inclusion in this study of addiction in rats.

² Payne, *J. Pharm. Exp. Therap.*, 1935, **53**, 401.

A 2% suspension of the drug in 2% gum acacia was administered daily by stomach tube in doses of 50, 100, and 200 mg. per kg. for a period of 3 months. Such doses are large even for the rat, being respectively 4, 8, and 16 minimal effective doses (M.E.D. in yeast fevered rats, 12.5 mg. per kg.³). No evidence of addiction was found; the 24-hour withdrawal irritability closely followed that of the controls receiving 2% gum acacia solution alone.

Experimental evaluation of insulin in the treatment of morphine abstinence hyperirritability: Several favorable clinical reports of the efficiency of insulin in relieving the symptoms of morphine withdrawal^{4, 5} suggested a trial of its ability to relieve abstinence hyperirritability in rats.

The 24-hour withdrawal hyperirritability of rats addicted for periods of 4 to 5 weeks on ascending doses of morphine sulphate was treated with graded doses of insulin and the struggle response before and after treatment compared. The results were inconstant at various doses but median results were about the same as those produced by the injection of tap water.

An attempt was also made to alter the course of addiction and tolerance by the daily administration of insulin. One hour before the daily dose of morphine, insulin was injected in a dosage shown to produce a marked (but in no case fatal) hypoglycemia. No effect on either addiction or tolerance could be shown; addiction developed at the same rate and to the same degree in animals receiving morphine-insulin as in those receiving morphine-tap water. The rate and magnitude of tolerance development was likewise essentially identical in the 2 groups.

³ Smith and Hamburger, *J. Pharm. Exp. Therap.*, 1935, **54**, 346.

⁴ Sakel, *Ztschr. f. d. ges. Neurol. u. Psycho.*, **129**, 639; *ibid.*, **143**, 506.

⁵ Braun, *Schweiz. Arch. f. Neurol. u. Psych.*, **27**, 226.