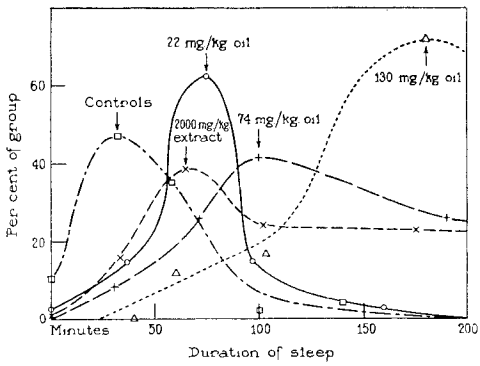
Synergism of Cannabis and Butyl-Bromallyl-Barbituric Acid

*By S. Loewe**

Preparations of *Cannabis americana*, when administered alone, do not produce unequivocal effects in the albino mouse (1). In studies undertaken to determine whether Cannabis gives clearer results when administered in combination with other drugs, it was found that no appreciable synergism or antagonism results in combinations with stimulants, but that Cannabis caused a definite depressant action when given with a hypnotic. Data on the synergistic action of Cannabis preparations and butyl-bromallyl-barbituric acid (Pernoston) from 323 experiments on adult male mice will be summarized in this report. Barbital was employed as a synergist in 29 additional experiments not recorded here, but was found to be far less effective.

EXPERIMENTAL

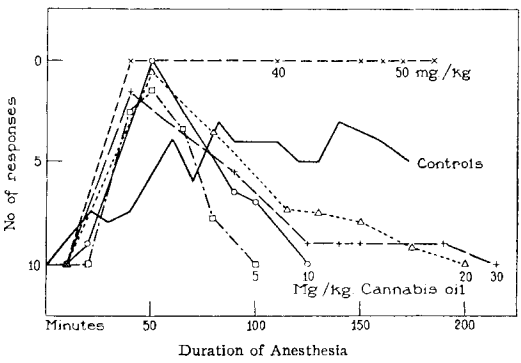
The Cannabis preparations were administered by stomach tube followed by the hypodermic injection of the hypnotic (0.67% aqueous solution of Pernoston Sodium, or 2% of Barbital Sodium). A highly potent purified Cannabis oil was available[1] which yielded a stable aqueous suspension when triturated with glucose and tragacanth. Except for a few exploratory experiments in which 45 mg. were used (groups I and VI of Table I) Pernoston was uniformly administered in the threshold hypnotic dose, *i. e.*, 60 mg. per Kg. Cannabis was found ineffective to produce any perceptible hypnotic action even in high doses, when administered alone (groups III*A* and III *B*), but caused a marked increase in the hypnotic effect of Pernoston as measured by the period of suppression of the righting reflex (duration of "sleep"). The relation betweeen the dose of Cannabis and the duration of "sleep" is shown in Graph 1, where the individual curves represent the average effects produced in each group of experiments with different



Graph 1. Variations of the Duration of Sleep with varied Cannabis Doses.—Incidence (per cent of mice of each group; ordinate) of the durations (abscissa) of hypnotic action of the same pernoston dose when administered alone (·———· = Controls) or combined with average doses of 22 mg. (———), 74 mg. (— — —), 130 mg. (. . . . .) of Cannabis Oil or 2000 mg. of Cannabis Extract I (– – – –)per Kg.

amounts of the drug. Further details of the various experiments are summarized in Table I.

The Pernoston dose/sleep duration curve is relatively steep in the range of dosage close to and above 60 mg. per Kg. When expressed in Pernoston equivalents, the synergistic effects surveyed in Table I fall within the range 60 to 90 mg. per Kg.



Graph 2. Increase in Intensity and Duration of Corneal Anesthesia in Mice with varied Doses of Cannabis. — Ordinate: Number of reflex responses to 10 subsequent touches of cornea. Abscissa: Time interval from administration of Cannabis dose.—Each curve represents average from 5 experiments with the same Cannabis dose (mg. per Kg. = figure at single curve); all animals received additional 60 mg. per Kg. Pernoston except those of control curve (Ctl.) with 62 mg. per Kg. Cannabis Oil.

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[1] Through the courtesy of Dr. R. P. Walton; origin and potency of this distillate oil are described in his paper (3).

Other features of the action of Cannabis in combination with Pernoston were: (*a*) the more rapid onset of the hypnotic action, and (*b*) corneal anesthesia. The latter effect is comparable to that produced by *Cannabis indica* on the cornea of the rabbit (2). The depth of the anesthesia was estimated by counting the number of reflex responses to ten subsequent touches of the cornea with a bristle at regular intervals. However, both of these effects require higher doses of Cannabis for their production than those prolonging the hypnotic sleep.

when the extract was boiled with water for 72 hours (see group VIII, Table I). Furthermore the same relative potencies of Cannabis oil and extract I were found in tests in the mouse and in the dog: 25 tests in the dog showed the extract to have about 1/200 of the potency of the oil, and a very similar ratio is indicated by the mouse tests in the figures given in Table I (compare groups IV and V).

The minimum dose of Cannabis oil giving a distinct effect in the mouse lies between 10 and 20 mg. per Kg., *i. e.*, less than 0.4 mg. per animal; whereas, in the dog test,

Table I.—Duration of Hypnotic Action after Varied Doses of Cannabis and Pernoston

Experimental Group	Dose in mg. per Kg. Cannabis	Dose in mg. per Kg. Pernoston	Number of Expts.	Righting Reflex Suppressed for over 50 Min., Per Cent	Righting Reflex Suppressed for over 70 Min., Per Cent	Righting Reflex Suppressed for over 100 Min., Per Cent
I. Control	0	45	10	20	0	0
II. Control	0	60	68	28	9	4
III*A*. Control	62[a]	0	10	0	0	0
III*B*. Control	3400[b]	0	8	0	0	0
IV. Cannabis Oil	22[c]	60	36	81	29	10
Cannabis Oil	74[c]	60	24	92	71	33
Cannabis Oil	130[c]	60	18	100	89	78
V. Cannabis Extract I	1000	60	20	45	15	5
Cannabis Extract I	2000	60	70	79	51	29
VI. Cannabis Extract I	2000	45	9	33	22	11
VII. Cannabis Extract II	0	60	10	40	20	10
Cannabis Extract II	1000	60	10	40	0	0
Cannabis Extract II	2000	60	10	70	20	20
VIII. Cannabis Extract I, 72 hr. boiled	2000	60	10	0	0	0

[a] Cannabis oil. [b] Highly potent extract. [c] Average of doses between 10 and 40 mg., 50 and 82 mg. and 100 and 163 mg. per Kg., respectively.

A comparison was made of the action of a commercial extract of Cannabis.[2] This extract was found to produce the same synergistic action, varying with the dosage (Table I, groups V and VI). An example of the assay of the depressant principle of Cannabis on the mouse is shown in group VII of Table I. The procedure was applied to another lot of the same commercial extract (extract II) which was found to have approximately the same potency as extract I.

Proof that the active principle giving the mouse response is identical with the unidentified narcotic Cannabis principle, assayed on the dog, requires further investigation. Two observations are in favor of this assumption: The thermostability of the Cannabis principle, as indicated by the dog test, is limited, and the same is true of the principle revealed in the mouse. The effectiveness on the mouse was completely lost

[2] Kindly furnished by the Commissioner of Narcotics, Treasury Department, Washington, D. C.

from 2 to 10 mg. per Kg., or from 10 to 100 mg. per animal are required. Thus the mouse test requires only from 1/25 to 1/250 of the amount of Cannabis used in the dog assay method.

REFERENCES

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