

*Citation:*

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**Physiology.** — “*Researches on scopolamin-morphin narcosis*”. By Dr. W. STORM VAN LEEUWEN and Miss M. V. D. MADE. (Communicated by Prof. MAGNUS).

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Much work has been done on scopolamin-morphin narcosis ever since SCHNEIDERLIN <sup>1)</sup> introduced it into medical practice (1900). One of the principal questions that occupied the workers in this field was, whether the administration of a mixture of these two poisons brings about a “potentiated synergism”, which BÜRGI defines as being a stronger effect of a mixture of poisons than the action the component parts alone could lead us to expect. In order to ascertain whether in the scopolamin-morphin mixture “potentiation” occurs, HAUCKOLD <sup>2)</sup> has performed many experiments with rabbits, KOCHMANN <sup>3)</sup> with dogs and SCHNEIDERLIN with men.

HAUCKOLD administered subcutaneously to rabbits respectively morphin, scopolamin, and morphin-scopolamin and detected “potentiation”. He recorded that 5 mgr. of morphin + 0,5 mgr. of scopolamin per kg. can produce narcosis in a rabbit, while 10 mgr. of morphin and 200 mgr. of scopolamin injected separately did not produce a narcotic effect. From this HAUCKOLD concluded that, though scopolamin *per se* does not bring about narcosis in a rabbit, it is nevertheless capable of activating a non-narcotic morphin-dosis. This assertion, however, appeared to be based on erroneous observation, first because we have demonstrated by a method to be discussed lower down, that 0,5 mgr. of scopolamin as well as 5 mgr. of morphin produce decidedly a narcotic effect and secondly, because also with HAUCKOLD’s method, we found no potentiation, but merely simple addition of effects.

HAUCKOLD administered the scopolamin, the morphin, and the mixture scopolamin-morphin to rabbits subcutaneously and then

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<sup>1)</sup> SCHNEIDERLIN. Eine neue Narkose. Ärtzl. Mitt. aus u. für Baden. Mai 1900, quoted from HAUCKOLD SCHNEIDERLIN. Die Skopolamin-Morphin-Narkose. Münch. Med. Wochenschr. 1903. N<sup>o</sup>. 9, pag. 371.

<sup>2)</sup> E. HAUCKOLD. Ueber die Beeinflussung von Narkoticis durch Skopolamin. Zeitschr. f. exp. Path. u. Ther. Bd. 7, pag. 743, 1910.

<sup>3)</sup> M. KOCHMANN. Ueber die therapeutischen Indikationen des Skopolaminum hydrobromicum. Die Therapie der Gegenwart. 1903, pag. 202.

ascertained whether or no a narcosis ensued. We have repeated these experiments, but since — as also HAUCKOLD observes — the depth of the narcosis is difficult to judge in rabbits, we altered the technique by administering on the same day the various poisons to a series of about twenty rabbits, almost simultaneously. Every quarter of an hour the condition of the animals was observed and noted down, the observer not knowing what poison had been injected into the animal under observation.

In this way we made the following experiments:

6 rabbits were given 10 mgr. of morphin per kg. subcutaneously.

6 rabbits were given 1 mgr. of scopolamin per kg. subcutaneously.

6 rabbits were given 5 mgr. morphin + 0,5 mgr. scopolamin per kg. subcutaneously.

All the animals were examined regularly during 2½—3 hours.

It thereby appeared that 1 mgr. of scopolamin had only a slight narcotic effect. The action of 10 mgr. of morphin was manifest; that of 0,5 mgr. of scopolamin + 5 mgr. of morphin was less marked than that of 10 mgr. of morphin alone; consequently "potentiation" was out of the question.

After this negative result we examined the narcotic effect of scopolamin and morphin also by another method. A so-called isolated rectusfemoris preparation was made on decerebrated rabbits and the influence was recorded of morphin, of scopolamin, and of morphin + scopolamin on the homolateral contraction-reflex of the rabbit. After a slight technical correction this method, which had already often been applied to cats <sup>1)</sup>, appeared to be well-adapted for rabbits.

The reflexes elicited in decerebrated rabbits by the faradic stimulus were registered on a Kymograph; and afterwards the results of every experiment were plotted. An instance of the influence of 5 mgr. of morphin on the homolateral contraction-reflex of the rabbit is given in Fig. 1.

In these experiments series of five rabbits were given 0,5 mgr. of scopolamin, or 10 mgr. of morphin or 0,5 mgr. of scopolamin + 5 mgr. of morphin and in all these cases the injections were not given till it appeared that the reflexes elicited by equi-intense stimulation were of the same magnitude. In case scopolamin + morphin was given, first the scopolamin was injected and 20 minutes later the morphin.

The effect of the injections on the magnitude of the reflexes were

<sup>1)</sup> W. STORM VAN LEEUWEN, Quantitative pharmakologische Untersuchungen über die Reflexfunktionen des Rückenmarks bei Warmblütern. I. Mitt. Pflügers Arch. Bd. 154, page 307. 1913. III. Mitt. Pflügers Arch. Bd. 165, p. 84. 1916.

noted for the scopolamin after 40 min., for the mixture scopolamin + morphin 40 min. after the scopolamin-injection, and for the morphin after 20 minutes.

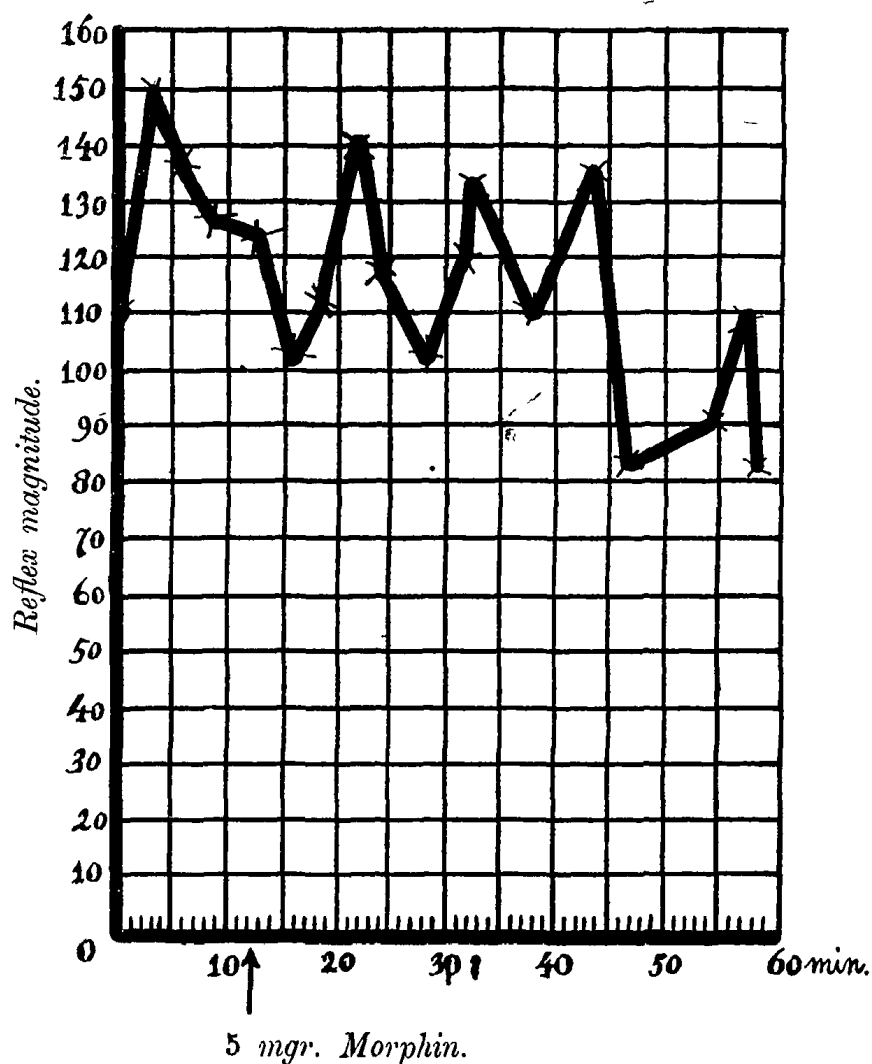


Fig. 1.

The results are as follows:

0,5 mgr. of scopolamin causes after 40 min. a decrease of 37 %,  
 5 mgr. of morphin " " 20 " " " " 15 %  
 0,5 mgr. of scop + 5 mgr. of morphin causes after 40 minutes a  
 decrease of 32 %.

These percentages require correction, as it appeared from a number of control-experiments that the magnitude of the reflexes diminishes spontaneously if no poison is administered, viz. 9 % after 40 minutes and 4 % after 20 minutes, so that the above values are respectively 28 %, 11 % and 23 %.

It is evident therefore, that also if this procedure is followed there is no trace of "potentiation", the value obtained in the mixture-experiments not being higher, but lower than the sum of the actions of morphin and scopolamin separately.

HAUCKOLD and many others assume that small doses of scopolamin do not anaesthetize a rabbit. Our experiments go to show that 0.5 mgr. of scopolamin has a distinct narcotic effect upon the magnitude of the reflex. In conjunction with Dr. G. LILJESTRAND we ascertained the influence of various doses of scopolamin on a spinal reflex of the decerebrated rabbit. The result was that this narcotic effect does not increase continually with an increase of the dosis, but soon reaches an optimum and even decreases again after this (see fig. 2 firm line). It seems that with the higher doses a stimulating effect is added to the narcotic effect.

It might be generally assumed that a twice larger dosis yields a twice stronger effect. This, however, is not the case with many of the alkaloids. When plotting the relation between the dosis per kg. of the animal and the effect of such a poison, the doses along the *abscissae* and the (narcotic) effect along the *ordmates*, a curve is produced, which first ascends abruptly, and then proceeds nearly horizontally. This is seen distinctly in fig. 2 (dotted line), borrowed from a paper by LILJESTRAND, V. D. MADE and STORM VAN LEEUWEN<sup>1)</sup>, in which the full line illustrates the narcotic effect of scopolamin in various doses (concentration-effect curve of scopolamin).

Besides HAUCKOLD, KOCHMANN also studied this problem. He experimented with dogs and believed that he had detected "potentiation". Because we did not succeed in finding "potentiation" either with HAUCKOLD's method, nor with the one commonly used at our institute (influence on reflexes of decerebrated animals), we have also put to the test KOCHMANN's experiments.

For this purpose series of from 3 to 6 dogs were given subcutaneously morphin, or scopolamin or morph. + scop. The doses were calculated per kg. animal.

An initial experiment was performed with the same dosis KOCHMANN had used. KOCHMANN asserts that 5 mgr. of morphin and 0.5 mgr of scopolamin (we suppose his doses to be given per kg. animal, though the writer does not say so) do not of themselves produce any narcotic effect on the dog, but that their joint action puts the animal under a profound narcosis. It must be argued that this occurred only in few cases. Our initial results seemed to substantiate KOCHMANN's findings, for it appeared that in a dog 5 mgr of morphin + 0.5 mgr

<sup>1)</sup> LILJESTRAND, V. D. MADE and STORM VAN LEEUWEN. Zur Konzentrations-Wirkungskurve des Skopolamins. Appears in *Pflügers Arch.* 1919.

of scopolamin exerted as strong an action as 10 mgr of morphin by itself, while 0.5 mgr of scopolamin exerts a stimulating rather

*Paralysing effect of Scopolamin on the homolateral contraction-reflex in the decerebrated rabbit.*

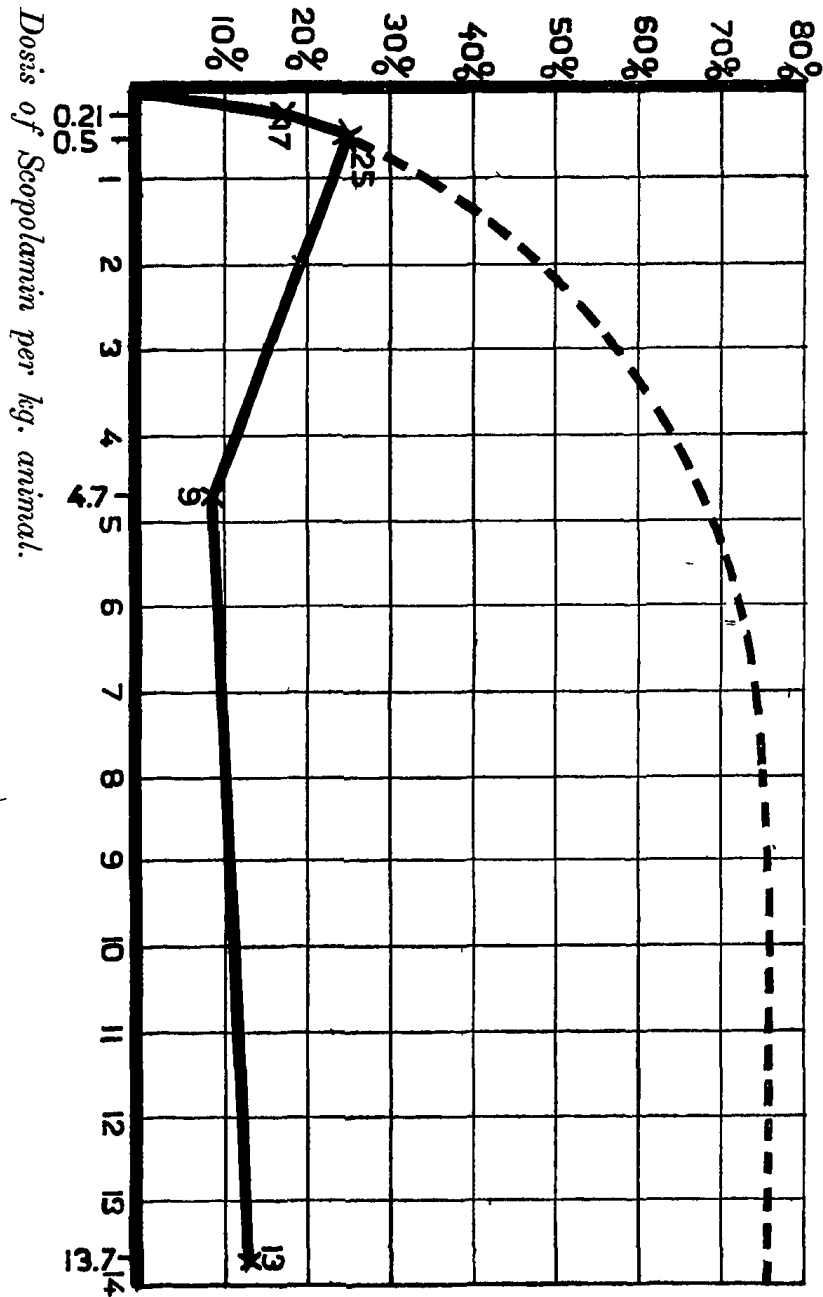


Fig. 2.

than a paralysing influence. On closer investigation it appeared, however, that the case is different, for when 5 mgr. of morphin was given alone (i.e. without scopolamin) its effect proved not to be different from that of 10 mgr. of morphin. This finding induced us

to investigate the action of different quanta of morphin on the dog. The results obtained were that doses smaller than 1,5 mgr. had but little narcotic effect or none at all; that 1,5 mgr. yields a distinct action, 2,5 mgr. a narcotic action, which is considerably stronger, while the effect of 5 mgr. differs little from that of 2,5 and finally that, as said above, the influence exerted by 10 mgr. is about equal to that of 5 mgr. If we should draw a curve of this peculiar relation between action and concentration, a so-called concentration-effect curve, it would again rise abruptly at the outset and then again proceed about horizontally, just like the curve representing the action of morphin and of scopolin on the reflexes of the rabbit.

After it had thus appeared that the action of 5 mgr. of morphin + 0,5 mgr. of scop. agrees with that of 10 mgr. of morphin, but still is not greater than that of 5 mgr. of morphin alone, we tried to find out whether the action of smaller doses of morphin was intensified by scopolamin. An injection of 2,5 mgr. of morph. per kg. was given to two dogs I and II, and to two other dogs III and IV 2,5 mgr. of morph. + 0,5 mgr. of scop. per kg. was administered. The narcosis of dog III was as profound as that of I and II, but that of IV was considerably *less* profound than that of I and II. The inevitable conclusion, therefore, is that scopolamin inhibited the action of morphin, so it did not bring about "potentiation" at all. This result was confirmed by a series of experiments with dogs, in which some received 1,5 mgr. of morphin and others 1,5 mgr. of morph. + 0,5 mgr. of scop. The narcosis with the former group was invariably more profound than that of the second.

It follows from these experiments that although narcotic symptoms are generated by scopolamin in doses of from 0,5 to 1 mgr. per kg., this poison has also a distinct stimulating effect on the dog. When small doses of morphin are mixed with scopolamin, the result is the algebraic sum of the effects of the two components and the narcotic effect of the morphin antagonizes in part the stimulating effect of the scopolamin. With larger doses of morphin the stimulating effect of the scopolamin falls back, while it would seem that the narcotic effect of morphin is sometimes reinforced in a small degree by the scopolamin, however in such a small degree that it cannot be called "potentiation", but is merely to be considered as a simple addition.

Upon the evidence founded upon very accurate experiments SCHNEIDERLIN concluded that in men the scop-morph. combination produces a real "potentiated" narcotic effect. He administered a rather

large dosis of morphin to some patients, after a few days a dosis of scopolamin, and again some days later half the dosis of each poison. In control-experiments, some patients were first given the morph. + scopol. and afterwards the two poisons separately. In all cases the administration of the mixture resulted in a general narcosis, which did not occur after morphin or scopolamin alone. This then is a case of true "potentiation".

This finding does, however, not yield great profit for the clinic, since this result is not always obtained and, as to sensitiveness to scopolamin, patients differ too much to render a correct dosage possible.

#### *Summary.*

Morphin produces a narcotic effect in rabbits, in dogs (and also in men), but the curve representing the relation between dosis and effect is a parabola, which means that with the smaller doses a small increase in the doses causes a considerable increase in the narcotic effect, whereas with the larger doses a similar increase of dosis brings about a much smaller increase of the narcotic action.

Scopolamin narcotizes the rabbit. The concentration-effect curve concurs with that of morphin. Its stimulating effect is obvious in the dog, in man its action is evidently narcotic.

No "potentiation" is obtained in the rabbit with the scopolamin-morphin mixture, either by our reflex-method or by HAUCKOLD's method. Neither was "potentiation" dedected in the dog.

According to SCHNEIDERLIN "potentiation" occurs in man, but it is presumably not constant.