

tracts of corpus luteum consists of cholesteryl palmitate, potassium stearate, possibly a very slight amount of cholesteryl stearate and free fatty acids.

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THE ANTISPASMODIC ACTION OF CHLORETONE.*

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Several years have now passed since Macht and his co-workers began their systematic pharmacological and clinical study of the action of the benzyl compounds—particularly benzyl benzoate and benzyl alcohol. In a series of articles beginning with his study of one group of the opium alkaloids Macht¹ logically deduced from his study of the other group that the benzyl component of the molecule must be responsible for the inhibitory and tonus lowering properties of the group as represented by papaverin. His subsequent investigation² of benzyl benzoate, benzyl acetate, benzyl alcohol³ and finally benzyl mandelate⁴ seemed to prove that in these compounds he had discovered very active antispasmodics whose therapeutic value was greater than any such drug previously discovered.

In considering the work of Macht on the benzyl compounds it seemed that other active sedatives had been largely overlooked. Knowing the powerful action of chloretone (tri-chlor-tertiary butyl alcohol, $C_4H_7OCl_3$) as a sedative, hypnotic antiseptic, local anesthetic and general anesthetic, it seemed more than probable that it would possess marked antispasmodic action as well. Accordingly a long series of experiments were begun in which a direct comparison could be made between the action of benzyl alcohol and chloretone. The sister bromine compound to chloretone, namely, brometone, was also included in part of the work. Benzyl alcohol was chosen for comparison because of the insolubility of the esters and because it is generally agreed that the esters are hydrolyzed into benzyl alcohol during the process of absorption from the alimentary tract and that it is consequently the action of benzyl alcohol which is observed.

ACTION ON ISOLATED SMOOTH MUSCLE.

The first series of experiments were conducted upon strips of isolated smooth muscle such as the uterus, intestine and ureter, but particularly the uterus of the virgin guinea pig.

A summary of six successful experiments on the isolated uterus of the guinea pig gave the following comparisons as to amounts of the substances necessary to inhibit the normal tonus of the muscle.

On 9/12/22, 2 cc. of 0.5% chloretone solution added to 100 cc. of Locke's solution was much more effective than 2 cc. of 1% benzyl alcohol solution and about as effective as 5 cc. of 1% benzyl alcohol solution. In this experiment chloretone was 5 times as effective as benzyl alcohol.

On 9/15/22, 1 cc. of 0.5% chloretone solution was equivalent to 1 cc. of 2% benzyl alcohol solution and chloretone was therefore 4 times as effective as the benzyl alcohol. (See Fig. 1.)

On 9/19/22, 2 cc. of 0.5% chloretone solution added to 100 cc. of Locke's solution was more effective than 2 cc. of 2% benzyl alcohol solution but 1 cc. of 0.5% chloretone solution was less

* Scientific Section, A. Ph. A., Asheville meeting, 1923.

effective than 2 cc. of 2% benzyl alcohol solution. In this experiment chloretone was more than 4 times but less than 8 times as effective as benzyl alcohol.

On 10/31/22, 2 cc. of a 0.25% solution of brometone added to 100 cc. Locke's solution was not as effective as 1 cc. of a 0.5% chloretone solution. Also, 1 cc. of 0.5% chloretone solution was more effective than 1 cc. of 2% benzyl alcohol solution. In this experiment chloretone was more than 4 times as effective as benzyl alcohol and brometone slightly less effective than chloretone but about 4 times as effective as benzyl alcohol.

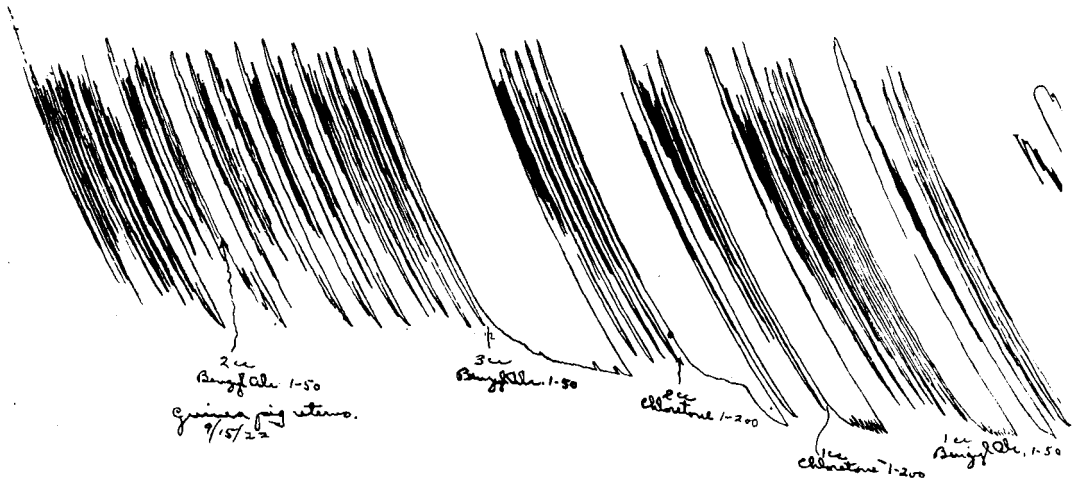


Fig. 1.—Isolated smooth muscle experiment—guinea pig uterus. Comparative action of benzyl alcohol and chloretone.

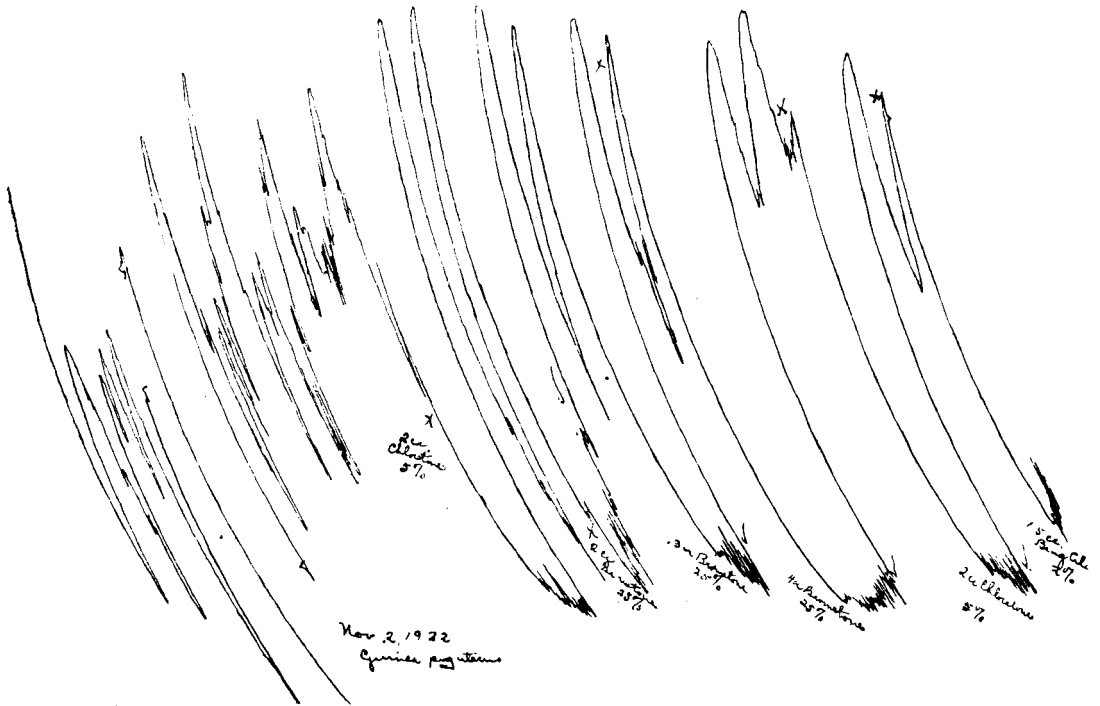


Fig. 2.—Isolated smooth muscle experiment—guinea pig uterus. Comparative action of brometone, benzyl alcohol and chloretone.

On 11/1/22, 2 cc. of 2% benzyl alcohol solution was more effective than 2 cc. of 0.5% chloretone solution and this latter solution was more effective than 2 cc. of 0.25% solution of brometone. In this experiment chloretone was less than 4 times as effective as benzyl alcohol.

On 11/2/22, 2 cc. of 0.25% solution of brometone was equivalent to 1.5 cc. of 2% benzyl alcohol solution. 2 cc. of 0.5% solution of chloretone was as good or better than 3 cc. of 0.25% solution of brometone and 2 cc. of 0.5% solution of chloretone was better than 1.5 cc. of 2% benzyl alcohol solution. In this experiment brometone was about 5 times as effective as benzyl alcohol and chloretone was about 4 times as effective. (See Fig. 2.)

In general the data from these experiments indicate that chloretone is fully 4 times as effective in inhibiting the tonus of the isolated uterus muscle as is benzyl alcohol and that brometone is from 4 to 6 times as effective as benzyl alcohol.

Experiments on the isolated intestinal strip indicate that 2 cc. of 0.5% chloretone solution when added to 100 cc. Locke's solution has a slightly greater inhibitory effect upon the contractions of the intestine than has 2 cc. of a 2% solution of benzyl alcohol. Chloretone is therefore a little more than 4 times as effective as benzyl alcohol. (See Fig. 3.)

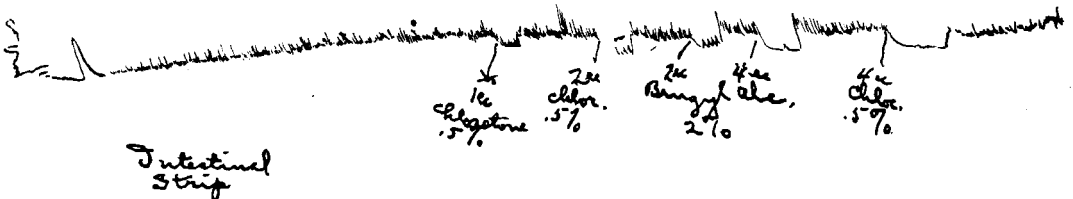


Fig. 3.—Isolated smooth muscle experiment—strip of guinea pig intestine. Comparative action of benzyl alcohol and chloretone.

On the isolated guinea pig ureter 0.5 cc. of 0.5% chloretone solution reduced the tonus but did not entirely inhibit the contractions. 3 cc. of 0.3% brometone solution entirely inhibited the contractions.

When the ureteral contractions were stimulated and increased by the addition of 1 cc. of barium chloride solution (1%) the addition of 2 cc. of 2% benzyl alcohol solution only partially inhibited the contractions while 2 cc. of 0.8% chloretone solution almost entirely inhibited the contraction. Certainly the chloretone is more than twice as effective as the benzyl alcohol on the isolated ureteral preparation.

ACTION ON PUPIL OF THE EYE.

A number of experiments were conducted on the excised frog's eye and also upon the intact rabbit's eye to determine the comparative mydriatic action of solutions of benzyl alcohol and chloretone.

On the excised frog's eye the action of solutions of benzyl alcohol of various strengths was found to be as follows:

A 2% solution caused first a marked contraction of the pupil which was rapidly followed by a maximal dilatation of the pupil.

A 1% solution caused marked dilatation of the pupil in three to six minutes becoming maximal in five or six minutes after immersion.

A 0.5% solution caused fair dilatation in eight to fifteen minutes but the action was never maximal.

Less concentrated solutions such as 0.25% and 0.2% caused only a slight mydriatic action which never even approached a maximal action.

Solutions of chloretone caused the following actions on the excised frog's eye:

0.6% and 0.8% solutions caused slow but maximal mydriatic action, beginning five to eight minutes after immersion and becoming maximal in about fifteen minutes.

0.5% solution caused a slow but marked dilator action which became definitely noticeable within ten minutes and reached a maximum in about 20 minutes.

0.4% solution caused a fair action in about 15 minutes becoming slightly more marked later.

0.2% solution caused a slight action in 15 minutes.

Brometone was tested in 0.3% and 0.2% aqueous solutions.

0.3% solution of brometone causes no noticeable dilatation of the pupil of the excised eye of a frog until about eight minutes after immersion. The action becomes more marked ten to fifteen minutes after and approaches the maximum fifteen to twenty minutes after.

The 0.25% and 0.2% solutions give a slightly slower action and do not cause more than a fair dilatation of the pupil.

These results on the excised eye of the frog would indicate that chloretone and brometone are not as rapid in their action as benzyl alcohol and that chloretone is not twice as effective as benzyl alcohol by this method of comparison. Brometone seems to be more active than chloretone, though not more than twice as active, and chloretone is fully as active as benzyl alcohol if not more so, though it is not twice as active.

On the intact rabbit a few drops of 0.8% solution of chloretone instilled into the eye caused a fair dilatation of the pupil in ten minutes. A few drops of a 0.3% solution of brometone caused a rather marked dilatation of the pupil in about ten minutes.

A 2% solution of benzyl alcohol caused a more rapid and more marked action on the pupil than that caused by the saturated solution of chloretone and brometone but a 1% solution of benzyl alcohol caused a more rapid action but no greater action than the 0.8% solution of chloretone.

The action of chloretone on the pupil of the rabbit's eye is slower in being evidenced but is more lasting and slightly more powerful than that of benzyl alcohol while brometone is the more powerful of the three by this method of comparison though its action is also slower but more lasting than benzyl alcohol.

ACTION ON THE INTACT INTESTINE.

A number of experiments were conducted upon rabbits, dogs and cats to determine the comparative action of chloretone and benzyl alcohol upon the intact intestinal loop according to the Trendelenburg method.⁵

The animals were anesthetized with paraldehyde, a 50% solution in olive oil being injected subcutaneously. Five dogs, six cats and four rabbits were used and several satisfactory experiments resulted from this number. The substances tested were injected intravenously usually in aqueous solution, but in a few instances larger doses of chloretone and brometone were injected in olive oil solutions.

On Nov. 8, 1922, an experiment on a dog showed that 4 cc. of 2% solution of benzyl alcohol (about 80 mg.) produced a very slight antispasmodic action and 200 mg. of chloretone produced a very marked effect.

On Nov. 9, 1922, in an experiment on a dog 10 cc. of 2% benzyl alcohol solution (about 200 mg.) produced a slightly greater effect than 20 cc. of a 0.5% solution of chloretone (100 mg.) but just equal to 40 cc. of a 0.25% solution of brometone (100 mg.). Also, 40 cc. of 2% benzyl alcohol solution (about 800 mg.) produced a greater effect than 40 cc. of 0.25% brometone solution (100 mg.).

On Nov. 13, 1922, in an experiment on a dog, 50 mg. of chloretone produced a greater effect than 100 mg. of benzyl alcohol. Fifty mg. of brometone were more active than 200 mg. of benzyl alcohol. Four hundred mg. of benzyl alcohol were very active, being more active than 100 mg. of chloretone.

In another experiment on a dog on Nov. 15, 1922, 200 mg. of benzyl alcohol produced greater action than 50 mg. of brometone.

On Jan. 12, 1923, in an experiment on a cat 2 cc. of 0.8% chloretone solution (16 mg.) were found to be about equal to 3 cc. of 2% benzyl alcohol solution (60 mg.).

On Jan. 30, 1923, in an experiment on a male cat the most satisfactory comparative results were obtained of any in the series. A reproduction of the tracing obtained in this experiment is shown in Fig. 4. In this experiment 0.08 cc. of benzyl alcohol caused a greater effect than 0.02 Gm. of chloretone but no greater than 0.04 Gm. of chloretone; 0.04 cc. and even 0.06 cc. of benzyl alcohol (No. 7) produced a greater effect than 0.03 Gm. of chloretone (No. 6), but 0.04 Gm. of chloretone (No. 8) produced fully as great an effect and the effect lasted a little longer.

In injections 9 and 10 the slightly greater and more lasting effect of 0.04 Gm. chloretone over 0.08 cc. benzyl alcohol is again demonstrated.

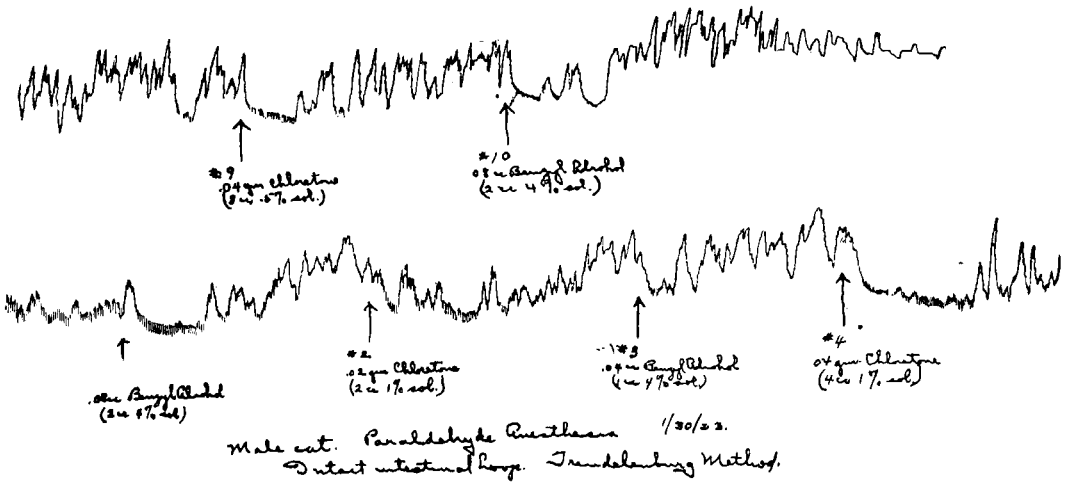


Fig. 4 (Parts 1 and 3).—Comparative action of benzyl alcohol and chloretone on the intact intestinal loop of the same animal.

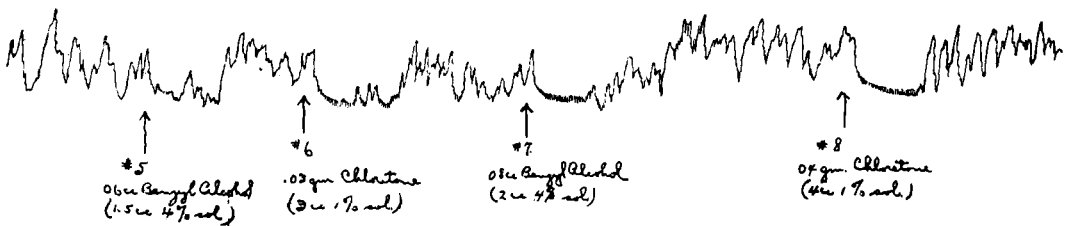


Fig. 4 (Part 2).—Comparative action of benzyl alcohol and chloretone on intact intestinal loop. 0.04 Gm. chloretone fully as active as 0.8 cc. of benzyl alcohol.

CONCLUSION.

In summarizing the experimental data it is quite apparent that by the isolated smooth muscle experiments and the tests on the intact intestinal loop chloretone is fully two to three times as active as benzyl alcohol and its effect is more lasting, while brometone is fully as active as chloretone in the small number of experiments in which it was included.

In the experiments on the excised frog's eye the action of benzyl alcohol is more rapidly evidenced than that of chloretone and brometone but is not as great as either of these substances though its action is in general greater than one-half that of chloretone.

From the comparative data obtained in all the tests it seems fair to conclude that chloretone is fully twice as active as benzyl alcohol and that its effect is more lasting. Also, that brometone is about as active as chloretone though somewhat handicapped by being much less soluble.

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TINCTURE OF GINGER.

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The experiments described in this paper were undertaken primarily in behalf of the pharmacopœial revision. The purpose was to determine the extent of the extraction of the ginger obtained by preparing tinctures with menstrua of different proportions of alcohol and the possibility of reducing the alcoholic percentage in the official formula. Also the feasibility of adopting for the U. S. P. the so-called "double strength" tincture prescribed by Treasury Decision No. 3092. Further, what should be the proper requirements for the standard preparation to be specified in the formula adopted for the U. S. P. X.

J. P. Snyder (*American Journal Pharmacy*, April 1918, p. 253) reviewed the published work of several other investigators on this subject and criticized the official standards and tests. He concluded "that it was possible to prepare Tincture of Ginger by the U. S. P. IX formula, in which the percentage of water-soluble solids is in excess of the 15 per cent. limit of the U. S. P. Further, that this percentage of water-soluble constituents is variable, depending upon the length of time the water is allowed in contact with the solids and also, to a great extent, upon the manner in which the solids are brought in contact with the water, and if this test serves any practical purpose and is to be retained, the U. S. P. should state the way and manner in which it is to be obtained."

He also criticizes the official directions for obtaining the total residue and contends that to prevent adulteration the minimum as well as the maximum for total solids should be given.

Under the title *Zingiberis* the U. S. P. IX describes five commercial varieties of ginger named in accordance with their geographical source, but it directs that the Jamaica Ginger only is to be used in preparation of the fluidextract and the tincture. The question arises why should standards be given for commercial varieties that are not used in medicine or that are actually prohibited in the official