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Full responsibility is assumed by the writer, however, for any errors in presentation, results or conclusions which may appear in this report.

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SOME PHARMACOLOGICAL AND BACTERICIDAL PROPERTIES OF UMBELLULONE.*[1,2]

BY MILES E. DRAKE[3] AND ERNST T. STUHR.

INTRODUCTION.

The literature on the oil of the California laurel, *Umbellularia californica* (Hook. and Arn.) Nutt., includes very little information on the pharmacology of the oil, or of the ketone (umbellulone) obtained from it. Likewise, no reference was

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* Scientific Section, A. PH. A., Washington meeting, 1934.

[1] An abstract based upon a thesis by Miles E. Drake submitted to the faculty of the Graduate School of the Oregon State College, in partial fulfilment of the requirements for the degree of Master of Science in Pharmacy.

[2] Department of Pharmacology and Pharmacognosy, School of Pharmacy, Oregon State College.

[3] Fairchild Scholar, 1933.

found in the literature on volatile or essential oils in regard to the germicidal or fungicidal activity of this oil and ketone. Extensive research has been pursued on the chemistry of the constituents in this oil by various investigators.

Persons who have come in close proximity with the myrtle oil or its vapors report discomforts, such as severe headaches, irritation of the skin and mucous membrane, and in several instances unconsciousness resulted. The apparent potency of the oil prompted this investigation.

HISTORICAL.

Umbellularia californica (Hook. and Arn.) Nutt. was first collected in California by Menzies (1) in the latter part of the eighteenth century. Prior to Menzies, the Spaniards of California knew the tree as *Laurel Silvestre*.

In 1826 Douglass (2) classified this evergreen tree as a laurel, *Laurus regia* (the regal laurel) probably intending to indicate the beauty and splendor of the tree.

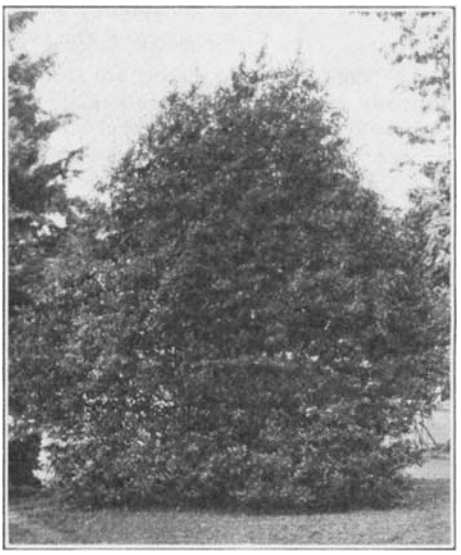


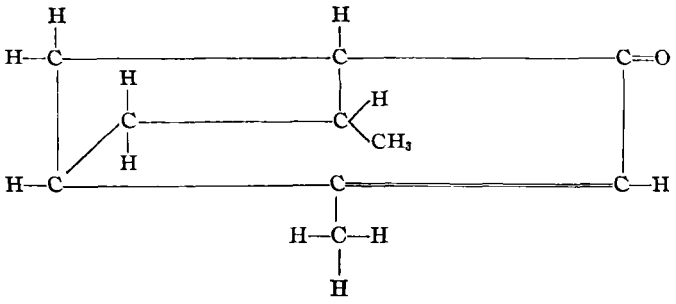
Fig. 1.—Myrtle Tree (*Umbellularia californica*).

In 1833 Hooker and Arnott (3) classified this evergreen as *Tetranthera californica*. Later Nuttal (3) gave it the present name of *Umbellularia californica*. As far as has been reported this is the only representative of the genus *Umbellularia*.

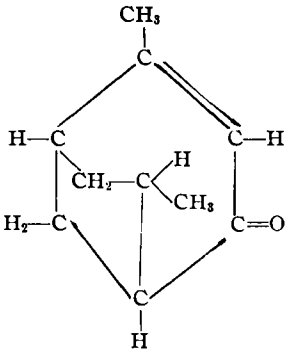
Heaney (4) in 1875 by fractionation under reduced pressure obtained from the oil of the California laurel a colorless liquid (Oreodaphenol) possessing a pungent odor.

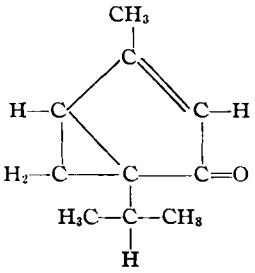
Stillman (5) in 1880 by fractionation at 215–216° C. obtained a colorless mobile liquid possessing an aromatic but pungent odor. Excessive inhalations of the vapors of this fraction were observed to produce headaches.

Powers and Lee (6) in 1904 reported the following principles or constituents which the oil yielded on fractionation: pinene, cineol, eugenol, methyl eugenol and a ketone, umbellulone, which was collected at 217–222° C. The purified ketone had a sp. gr. of 0.9584 at 15/15, $[\alpha]_D - 37°$ in a 100-mm. tube. Powers and Lee (6) concluded that umbellulone had one ethylenic linkage, and gave it the following structural formula:



Tutin (7) in 1908 gave umbellulone the following structural formula:





Semmller (8) in 1908 gave umbellulone the structural formula which is accepted to-day. According to Spiegel (9), sabinol, thujone and umbellulone are very similar in structure.

DISTILLATION AND DESCRIPTION OF THE OIL OF MYRTLE.

The leaves after drying are steam distilled. The oil is collected in an excess of water distillate which on standing separates into two layers, the oil layer being on top of the water layer. The layer of oil is decanted and dried over anhydrous sodium sulphate. The yield of the oil, according to Parry (10), varies from 2.5 to 5.5 per cent.

The oil of *Umbellularia californica* is a clear brownish yellow liquid. It possesses a sweet but pungent, irritating, empyreumatic, persistent odor. Parry (10) gives this oil a sp. gr. of 0.935 to 0.950, and an optical rotation of −22°. Sawyer (11) states that the dry oil has a sp. gr. of 0.936, and a solubility of 1:1000 in water.

THE KETONE FROM THE OIL OF MYRTLE.

Wienhaus and Todenhofer (12) in 1929 prepared the ketone, umbellulone, from the oil of myrtle by preparing a water-soluble sulphite addition product from the oil. This addition product was steam distilled and purified by fractionation under reduced pressure. Following the method of Wienhaus and Todenhofer no appreciable ketone yield was obtained; therefore, the following modified method was employed.

Method No. 1. Modified Wienhaus and Todenhofer.—Three hundred and fifty grams of myrtle oil were shaken out twice with a saturated solution composed of 400 Gm. of sodium sulphite and 80 Gm. of sodium bicarbonate in 400 cc. of distilled water. This solution when neutral to five drops of phenolphthalein was shaken vigorously for 30 minutes. The resulting mixture was allowed to separate and the oil layer was decanted. This oil was then treated with a second 400 cc. of the saturated sodium sulphite-bicarbonate solution and permitted to stand 24 hours. The oil was again decanted, and the aqueous portions of the first and second washings were combined and steam-distilled in a neutral condition for two hours in order to free the aqueous solution of any excess oil. The oil-free aqueous residue was treated with 40 Gm. of stick sodium hydroxide and the mixture was steam distilled for three hours. The resulting product was fractionated under 4-mm. reduced pressure, yielding purified umbellulone at 77.5–77.8° C. (uncorrected). Yield 48 Gm.

Physical Constants of the Ketone (Umbellulone).—$[\alpha]_{D21}$ −38.50; n_D 1.48285; d_{25}° 0.9465, agreeing fairly well with the reports of Wienhaus and Todenhofer (12).

The following tabulation gives the constants reported by various investigators.

TABLE I.

	Sp. Gr.	Op. Act.	R. I.	B. P. 4 Mm.
Wienhaus and Todenhofer (12)	0.949 (20°)	−38.51	1.48315 (20°)	85°
Stillman (5)		−36.30		
Powers and Lee (6)	0.9614 (15.5°)	−36.33	1.18325 (20°)	
Authors	0.9465 (25°)	−38.50	1.48285 (20°)	77.5–77.8°

Method No. 2. Fractionation.—Three hundred grams of myrtle oil were fractionated at 4-mm. reduced pressure. A total of nine fractions was collected. Fraction IV (74–78° C.) and Fraction V (78–80° C.) were refractionated. Fraction No. 2 (77.1–77.6° C.) of IV, and fraction No. 1 (77.2–77.7° C.) of V were combined and refractionated, yielding 61 Gm. of the ketone, umbellulone at 77.1–77.7° C. Only two physical constants were taken of this fraction. The B. P. by the capillary method (13) was found to be 216–217° C. (corrected). The refractive index was found to be 1.4830 at 21° C. Yield: The following percentages of ketone yield were obtained:

Modified Wienhaus and Todenhofer method	13.71%
Fractionation method	20.3%

as compared to yields reported by previous investigators:

Wienhaus and Todenhofer (12)	24.5%
Powers and Lee (6)	60.0%
Stillman (5)	40.0%
Russell (14)	28.0%

SOLUBILITY OF UMBELLULONE.

Freely soluble in 70 per cent alcohol	Freely soluble in liquid petrolatum
Freely soluble in olive oil	Freely soluble in Miller solvent (19).

PRELIMINARY INVESTIGATION.

Effects on Blood in Vitro.—To determine the action of umbellulone on defibrinated blood *in vitro* the method of Dessemontit (15) was used. To one cc. of blood was added three cc. of 0.9% sodium chloride and 0.06 cc. of umbellulone. This mixture was warmed gently, placed in a Sedgwick counter and observed through a spectrometer. Horse blood and guinea-pig blood were used.

Results:

Diluted horse blood—no bands were present within range of methemoglobin.

Diluted horse blood plus 10% solution of potassium ferricyanide—upon heating gently the blood became a chocolate brown and the following bands were noted:

First Trial.		Second Trial.	
First band	635–631 μ μ	First band	636–632 μ μ
Second band	588–572 μ μ	Second band	587–572 μ μ
Third band	554–532 μ μ	Third band	544–532 μ μ

Diluted horse blood plus 0.06 cc. of umbellulone—upon heating the blood became a chocolate brown and the following bands were noted:

First Trial.		Second Trial.	
First band	635–631 μ μ	First band	634–631 μ μ
Second band	587–571 μ μ	Second band	589–573 μ μ
Third band	555–536 μ μ	Third band	554–532 μ μ

Diluted guinea-pig blood plus 0.06 cc. of umbellulone—the following bands were noted:

	First Trial.	Second Trial.	Third Trial.
First band	634–630 μ μ	634–631 μ μ	635–630 μ μ
Second band	586–572 μ μ	588–571 μ μ	589–572 μ μ
Third band	553–533 μ μ	553–534 μ μ	553–534 μ μ

The bands obtained on both horse blood and guinea-pig blood are in fair agreement with those reported by Halliburton (16). The center of the absorption band considered as characteristic had a wave-length of 630–634 μ μ, according to Dessemontit (15).

Effects on Blood in Vivo.—A guinea pig received two cc. of 1:1000 umbellulone in olive oil intraperitoneally three times a week for six weeks. At the end of six weeks the blood was obtained by the heart stab method and kept at 37.5° C. until used. To one cc. of this blood was added three cc. of 0.9 per cent sodium chloride solution. The results were as follows:

First band	634–630 $\mu\mu$
Second band	587–573 $\mu\mu$
Third band	554–532 $\mu\mu$

Figure 2 shows the absorption band at 630–634 $\mu\mu$. The guide lines above are the neon lines. (Page 203.)

Further work showed that umbellulone produced decided hemolysis of human, guinea-pig and horse blood.

Effects of Umbellulone upon the Intact Heart of the Frog.—The frogs were prepared for heart recording (17) and 0.2 cc. of 10 per cent umbellulone in 1 per cent acacia emulsion dropped upon the heart after a normal tracing had been obtained. Results:

Umbellulone at first produced a quickening in the heart rate which was followed by a progressive decrease in frequency, loss in tonus and a decrease in contraction of the ventricle. The heart finally stopped in diastole. It was found that the addition of 0.1 cc. of 1:1000 caffeine to the washed heart produced no reviving effect. The injection of 0.2 cc. of 1:1000 adrenaline hydrochloride into the right atrium also produced no reviving effect upon the paralyzed heart.

Effects of Umbellulone on the Atropinized Frog Heart.—The hearts of other frogs were first treated with 0.2 cc. of 1% atropine and the atropine allowed to take effect. About five minutes after the application of the atropine the excess was washed off with 0.65 per cent sodium chloride solution and 0.2 cc. of 10 per cent umbellulone dropped upon the heart. There was at first a quickening of the heart rate, which was followed by a progressive decrease in frequency, loss in tonus and a decrease in contraction of the ventricle. The heart stopped in diastole.

Effects of Physostigmine on Umbellulonized Frog Heart.—The hearts of frogs were treated with a 10 per cent solution of umbellulone. There was an initial increase of rate or frequency, followed by a progressive decrease in frequency, ending in apparent paralysis of heart. Several drops of 1:100 physostigmine solution were applied to the paralyzed heart, resulting in partial revival.

Effects of Umbellulone on Unanæsthetized Animals.—Injection:

Two guinea pigs were used, each receiving an intraperitoneal injection of four cc. of a 10 per cent solution of umbellulone in olive oil. Two minutes after the injection the guinea pigs showed a slight paralysis of the hind quarters. This was followed by a drop in pulse rate with a slight change in respiration which rapidly became very irregular. Both pigs showed asphyxia convulsions which became more frequent and pronounced toward the end of the experiment. Following the decrease in pulse rate there was a marked increase in the pulse which was followed by failure in respiration. The heart stopped in about a minute after respiration failure.

Post-mortem examination indicated the odor of umbellulone pronounced in both peritoneal and pericardial cavities. The heart stopped in diastole. The

heart, aorta and the superior and inferior vena cava were dilated. The lungs showed decided congestion and the blood was of a dark color.

Inhalation:

Warmed umbellulone was placed in a desiccator and allowed to vaporize in the presence of a guinea pig for a period of four hours. At intervals the enclosed chamber was oxygenated. The only apparent result was irritation of the mucous membranes of the eyes and nose. The respiration was at times irregular but at no time did it show signs of failure.

Experimental Work. I. Bactericidal Aspects.

Fungicidal action of the oil and the umbellulone.

Method:

The organisms used were *Monilia tropicalis* (1885) and *Trychophyton interdigetale* (2284).

The Food and Drug Administration method (18) was used with a standard loop for transferring to a broth of p_H 5.0 for a period of five days.

The solvent (19) employed to dissolve the ketone, umbellulone, was a sterilized mixture composed of 33 parts, respectively, of 95 per cent alcohol, glycerol, distilled water and 6.6 parts of powdered castile soap. This solvent was tested for fungicidal action and was found to check with the reports of Miller (19).

The fungicidal action of umbellulone was determined by a modification of the method by Kingery and Adkison (20). Two cc. of the ketone solution was placed in one cc. of 24-hour broth culture and allowed to stand for the specified intervals of time (one, thirty and sixty minutes), and then transfers were made to Sabouraud's Agar medium and incubated for 48 hours and read.

Ten experiments were undertaken. Table II is a tabulation of the typical results obtained.

Table II.

No.	Dilution.	Oil of Myrtle. Time in Minutes. 1.	30.	60.	Check.	Umbellulone. Time in Minutes. 1.	30.	60.	Check.
1885	1/10	−	−	−	++++	−	−	−	++++
	1/50	++	−	−	++++	−	−	−	++++
	1/100	++++	++	+	++++	+	−	−	++++
	1/1000	++++	+++	++	++++	++++	+	+	++++
2284	1/10	−	−	−	++++	−	−	−	++++
	1/50	+	−	−	++++	−	−	−	++++
	1/100	+++	++	+	++++	+	−	−	++++
	1/1000	++++	+++	++	++++	++++	++	++	++++

Legend to table:

−	No growth recorded.
+	1–4 colonies observed on the quarter.
++	5–10 colonies observed on the quarter.
+++	11–24 colonies observed on the quarter.
++++	25 or more colonies observed on the quarter.

The oil and the ketone in the absence of protein killed the specific organisms used in dilutions of 1:10 for intervals of 1, 30 and 60 minutes, but in a 1:50 dilution growth was recorded with one-minute contact for the oil of myrtle, but not for the umbellulone. In the 1:100 dilution there was recorded growth in all intervals of time for the oil of myrtle, while the ketone showed no growth on 60 minutes' contact. In 1:1000 dilution all contacts were positive.

The fact that the organisms were killed and not inhibited was demonstrated by taking a loop of each dilution for the various intervals of time, and transferring to a sterile tube of broth. No growth was recorded in 48 hours at 37° C.

FUNGICIDAL ACTION OF UMBELLULONE IN THE PRESENCE OF PROTEIN.

Fifteen experiments were undertaken.

Method:

Organisms (1885 and 2284) and the F. D. A. method (18) of transferring were used with the same technique as before, using media containing gelatin, peptone and 10 per cent defibrinated horse blood in Sabouraud's medium. The p_H for the respective media was adjusted to 5.5 and sterilized at 15 lbs. pressure for 18 minutes.

Results:

Blood Medium.—In the presence of 10 per cent blood medium, organism (1885) was killed for all contacts of time intervals by 1:10 dilution. 1:100 dilution was negative in 60-minute contact; 1:1000 dilution was positive in all contacts. The same results were recorded for organism (2284).

Gelatin and Peptone Media.—Organism (1885): All contacts were negative in 1:10 dilution; 1:100 dilution, 1-minute contact was positive, 30- and 60-minute contacts were negative; 1:1000 dilution, all the contacts of time intervals were positive.

Organism (2284): 1:1000 dilution on gelatin medium recorded positive in 1- and 30-minute contacts, while the 60-minute contact was negative. All other recordings were identical with those of organism (1885).

Umbellulone in the presence of protein-like materials was found to be only slightly inactivated.

NOTE: The dilutions as specified in all these experiments are as before adding to the 24-hour broth culture, in each case the original dilution was diluted one-half.

GERMICIDAL ACTION OF UMBELLULONE.

Method:

A. Wet Filter-paper method of the F. D. A. (18) was employed. Organisms used were *E. typhi* (Sears) and a standard stock culture of *Staphlococcus albus*. Neither organism was inhibited or killed by 5-minute exposures to 1:70 dilution of phenol. Both organisms were killed by a 15-minute exposure in a 1:90 dilution of phenol.

Results:

The accompanying Table III is typical of the results obtained.

TABLE III.

Organism.	Time.	Dilutions. 1:10	1:20	1:100	1:500	1:1000	1:2000
E. typhi	1	−	−	−	+	+	+
	2	−	−	−	+	+	+
	5	−	−	−	−	+	+
	7½	−	−	−	−	+	+
	15	−	−	−	−	−	+
	30	−	−	−	−	−	+
	60	−	−	−	−	−	+

Staph. albus	1	–	–	–	+	+	+
	2	–	–	–	+	+	+
	5	–	–	–	+	+	+
	$7^1/_2$	–	–	–	+	+	+
	15	–	–	–	–	+	+
	30	–	–	–	–	–	+
	60	–	–	–	–	–	+

Estimated phenol coefficient, 6.25.

B. The F. D. A. Agar-Plate Method (18).—E. typhi (Sears) and *Staph. albus* were the organisms used. The ointments were composed of: Umbellulone 10 per cent, 5 per cent, 1 per cent and 1:10 of one per cent, with lanolin as a base.

Results:

All dilutions showed inhibitory and diffusibility action. The fact that *E. typhi* and *Staph. albus* were killed was determined by using a portion of the material from the clear zone of the plate and transferring to sterile tubes of broth which were incubated for 24 hours at 37° C.

II. Effects of Umbellulone on Isolated Intestinal Segment.

The following experiments were carried out by using a modification of the procedure of Salant and Mitchell (21).

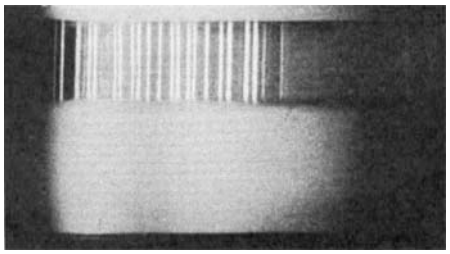


Fig. 2.—Spectrogram of the umbellulone on guinea pig blood.

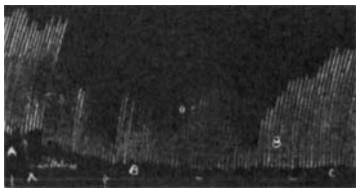


Fig. 3.—Rabbit gut. Effect of 1 cc. of 1/100 solution of umbellulone, giving a dilution of 1–40,000. (A) Normal; (B) Partial paralysis; (C) Normal segment. Base line indicates two-minute intervals.

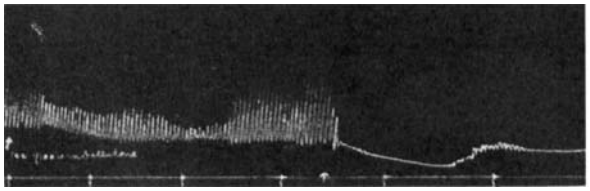


Fig. 4.—Rabbit gut. Showing progressive loss of contraction (in dilution of 1–13,333 of umbellulone), with period of slight stimulation and complete paralysis of intestinal segment. Time—two-minute intervals.

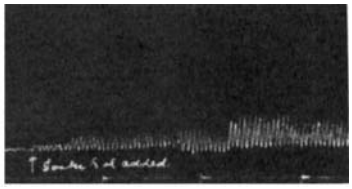


Fig. 5.—Rabbit gut. Intestinal segment revived in Locke's solution. Time—two-minute intervals.

Method:

The rabbits and cats were killed by administering an excessive dose of chloroform. The small intestines were immediately removed, care being taken to avoid injury to the intestines. The removed intestines were placed in fresh, oxygenated Locke's solution and kept at 37.5° C.

until used. The segments of the intestines (2.5 to 4 centimeters in length) were suspended in four hundred cc. of Locke's solution through which a stream of oxygen was bubbling continuously. The temperature was maintained at 37.5° C. by use of a constant temperature bath. Recordings were made on a single drum kymograph, using a Becker universal lever. The umbellulone was prepared in the form of a 1 per cent acacia emulsion. Dilutions of 1:10, 1:100 and 1:1000 were prepared for use in the experiment.

Results:

Both cat and rabbit gut when treated with a 1:100,000 dilution of umbellulone showed a slight stimulation with a slight increase in contraction, with tonus and amplitude remaining nearly constant.

Rabbit Gut.—Umbellulone in a dilution of 1:40,000 produced decided decrease in contraction (Fig. 3). In a dilution of 1:13,333 umbellulone produced a decided decrease in contraction, tonus and amplitude. This decrease was progressive in nature (Fig. 4). On washing gut with fresh Locke's solution the segment was revived (Fig. 5).

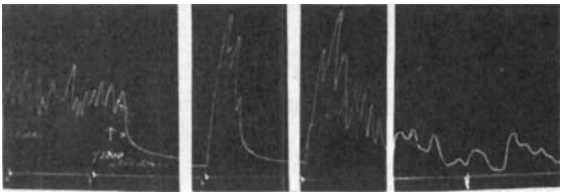


Fig. 6.—Cat gut. Effect of 1–5000 dilution of umbellulone on isolated intestinal segment. Time—two-minute intervals.

Cat Gut.—Umbellulone in a dilution of 1:5000 produced a progressive decrease in contraction, tonus and amplitude, finally resulting in paralysis of segment (Fig. 6). On washing gut with fresh Locke's solution the segment was revived.

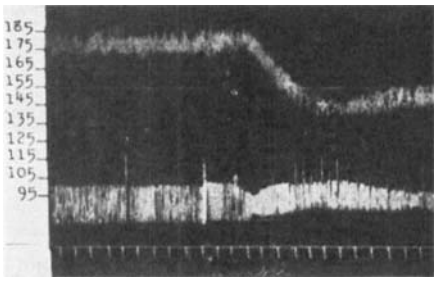


Fig. 7.—Dog. Blood-pressure and respiration. Normal B. P. from right carotid artery; normal respiration. Effects from femoral vein injection of 1 cc. undiluted umbellulone. Time—ten-second intervals.

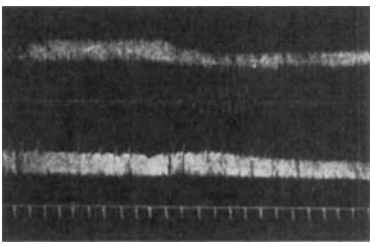


Fig. 8.—Dog. Blood-pressure and respiration. (Continuation of Fig. 7.) Progressive rise in B. P.; increased heart action; rapid (shallow) respiration, and intestinal stimulation. Time—ten-second intervals.

III. Effects of Umbellulone on Respiration and Blood Pressure.

Dogs were the only animals used in this work. A total of seven dogs was used.

Method:

The dogs were weighed and 1.2 cc. of 40 per cent chloretone in 40 per cent ethyl alcohol (22) per Kg. of body weight were injected intraperitoneally. Two and one-half hours later the dogs were prepared for blood pressure recording (23, 24) by using a Becker U tube mercury manometer for blood pressure and a Becker respiration plethysmograph for respiration. Both respiration and blood pressure were recorded on a single drum kymograph.

Results:

Umbellulone, when given intravenously, in a dose of 0.109 cc. per Kg. of body weight produced a rapid and decided fall in blood pressure (Fig. 7). This

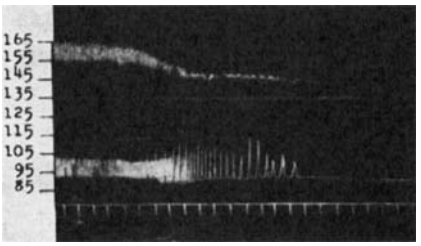


Fig. 9.—Dog. Blood-pressure and respiration. (Continuation of Fig. 8.) Second femoral injection (1 cc. undiluted umbellulone). Effects—failure of respiration, and arrest of heart beat. Time—ten-second intervals.

was followed by a progressive rise in the blood pressure which at no time regained the mean pressure (Fig. 8). The injection of a second dose of similar size, as stated above, produced death in a few minutes with failure in respiration followed by arrest of the heart (Fig. 9).

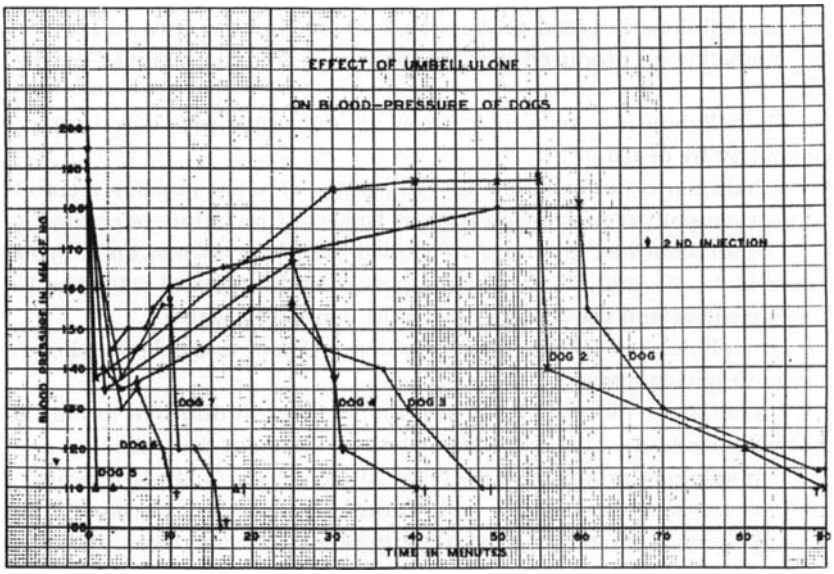


Fig. 10.

TABLE IV.—EFFECTS OF UMBELLULONE ON THE BLOOD PRESSURE AND RESPIRATION OF DOGS.

			10% Umbellulone in Olive Oil.				20% Umbellulone in Olive Oil.				Undiluted Umbellulone.				
	Normal.		10 Cc. Injection.		10 Cc. Injection.		7 Cc. Injection.		7 Cc. Injection.		1 Cc. Injection.		1 Cc. Injection.		Death Resulted.
Dog.	Resp.	B. P.	Resp.	B. P.	Resp.	B. P.	Resp.	B. P.	Resp.	B. P.	Resp.	B. P.	Resp.	B. P.	Min.
1	40	200	24	140	3	110									89
2	37	195	22	138	4	110									90
3	27	192					18	135	23	110					48
4	35	195					21	138	25	110					40
5*	28	190									5	110			3
6	58	187									156	135	18	110	9
7	72	180									66	138	12	112	16

* Received 2 cc. undiluted umbellulone intravenously.

TABLE V.—CHLORETONE ANÆSTHESIA COMPARISON ON DOGS.

Dog.	Age. Months.	Sex.	Weight, Kilos.	40% Chloretone. Cc.	Anæsthesia Time Minutes.
1	24	Male	17.0	20.4	8
2	12	Male	11.2	13.5	9
3	15	Female	11.2	13.5	8
4	10	Female	11.2	13.5	15
5	12	Male	11.3	13.8	8
6	9	Male	11.2	13.0	18
7	8	Male	9.7	11.0	20

NOTE: Time elapsing between injection of anæsthetic and operation was $2^1/_2$ hours in each case.

Post-mortem examination showed congestion of the lungs with blood clots. The heart stopped in diastole. The heart and the superior and inferior vena cava were dilated as were the other great vessels.

SUMMARY.

1. Umbellulone in blood produced methemoglobin *in vitro* and *in vivo.*
2. Umbellulone produced decided hemolysis of human, guinea-pig and horse blood.
3. Umbellulone injected intraperitoneally in guinea pig caused asphyxiation followed shortly by death.
4. Inhalation of umbellulone by guinea-pig irritated mucous membranes of eyes and nose caused irregular respiration at times but no failure of respiration.
5. Umbellulone in dilutions of 1:50 killed *Monilia tropicalis*, and *Trychophyton interdigetale* in 1-, 30- and 60-minute contacts. In dilutions of 1:100 the 1-minute contact was positive and the 30- and 60-minute contact negative.
6. Umbellulone in the presence of blood, peptone and gelatine showed but a slight loss in fungicidal power.
7. Umbellulone killed *E. typhi* and *Staph. albus* in dilutions as high as 1:500 for 15 minutes' contact. The estimated phenol coefficient was 6.25.
8. Umbellulone produced a decrease in frequency of the frog heart; loss of tonus and a decrease in the ventricle contraction. Stoppage of the heart occurred in diastole. Atropine, caffeine or adrenaline injected into the right atrium had no effect upon the paralyzed heart.
9. Results obtained on frog heart showed that umbellulone probably acts upon the same nerves and fibres as does atropine.
10. Umbellulone on isolated segment of rabbit and cat in 1:100,000 dilution produced slight stimulation; in dilutions of 1:40,000 or less, produced an apparent state of depression which progressed into partial paralysis. The length of time the paralysis was in effect depended on the degree of concentration of the solution; the more concentrated the solution the longer and the more complete the paralysis.
11. Intravenous injections of umbellulone caused a lowering of blood pressure and failure of respiration in dogs.
12. The clinical results and post-mortem examinations indicated that:

    a. Umbellulone probably acts as a depressant.
    b. Umbellulone produces rapid methemoglobin.

c. Umbellulone apparently caused pulmonary circulation to be blocked.

d. Umbellulone causes vaso-dilation of the heart and large vessels.

e. The minimal lethal dose of umbellulone in dogs is about 0.178 cc. per Kg. of body weight, death being due to failure of the respiration followed in a few minutes by stoppage of the heart.

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FURTHER STUDIES ON PSYLLIUM SEED.*[1]

BY HEBER W. YOUNGKEN.

In an article entitled "Studies on Commercial Psyllium Seeds" which appeared in Vol. XXI, No. 12, pages 1265–1273 of the JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION, the writer discussed some earlier studies he had made on various commercial varieties of Psyllium. Since that time he has examined new lots of Psyllium seeds imported from Spain and France. He has also studied plants with mature fruit and seed bearing spikes from growers of commercial Psyllium seeds in France and Spain, and has compared these materials with authentic

* Scientific Section, A. PH. A., Washington meeting, 1934.

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