kymograph. The muscle was suspended in a chamber filled with Locke's solution at 37°, and when peristaltic action was thoroughly established, 1 cc. of a solution of the ester was dropped into the chamber. A stream of oxygen which was kept bubbling through the cell served to distribute the solutions thoroughly. All liquid esters were made into 50 per cent solutions with alcohol, while the solid ones were made 20 per cent in alcohol.

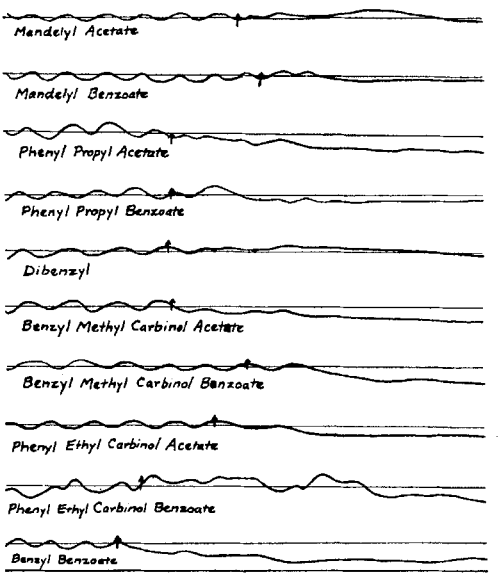

Chart I.

The results of the tests show that all the members of this series possess inhibitory or depressant action upon smooth muscle to about the same extent as does benzyl benzoate. It may be seen by the accompanying chart that in all cases the compounds caused cessation of peristaltic action, while in some instances there was a stretching of the muscle to a greater degree than when it was at the relaxed stage of the peristaltic movement.

COLLEGE OF PHARMACY,
UNIVERSITY OF WASHINGTON,
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CHEMICAL AND BIOLOGICAL ASSAY OF DRUGS.*

DIGITALIS STANDARDIZATION: UNDER ANESTHESIA.

BY J. B. BERARDI.

The action of drugs upon living organisms depends upon the state of the particular constituent parts, which go to make up the organisms. The state may be altered by seasonal variations, age, sex and previous administration of other drugs, etc. For example, when small doses of morphine are given in cases of broken compensation, the action of digitalis is altered. In some cases digitalis given in large doses prior to the administration of morphine produces no definite cardiac response, while in other cases, small doses of digitalis given after the administration of morphine produces full response.

The methods of standardization of digitalis, which are constantly receiving a great deal of consideration, utilize an animal which is anesthetized before standardization of the drug is carried out. The most commonly used is known as the Hatcher's cat method. In this method the preparation to be standardized, suitably diluted, is injected intravenously into an anesthetized cat.

Many objections have been raised to the use of these methods, the most outstanding one being that the death of the animal is produced by the anesthetic or

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hypnotic and not from the digitalis. In many cases it was found that respiration would stop before the heart ceased to beat. Another objection which is often raised is that the heart is so affected, either directly or indirectly, through its center in such a manner as to present a different digitalis action.

Ether and chloretone have been used in the standardization of digitalis. Both of these drugs affect the vagus center, hence produce an acceleration of the heart. It has been found that the same dose of digitalis when administered to an animal under anesthesia does not produce the same percentage of slowing in the heart rate; that in an anesthetized animal the dose required to produce death or toxic effects was considerably smaller than the dose necessary to produce toxic effects in the normal animal. L. W. Rowe found that the M. L. D. per kilo depends upon the degree of anesthesia. The lighter the anesthesia the more digitalis is necessary to produce death. If the drug is to be standardized for its therapeutic properties, then it should be standardized on a normal heart and not on one under anesthesia.

With these views in mind, the following therapeutic experiments were carried out:

A dog was carefully weighed. The normal heart rate was then determined by taking an average of four or five results at ten minute intervals. (It is important to get an accurate count without exciting the animal.) A definite amount of tincture of digitalis, diluted with physiological salt solution, was then given intravenously. After the injection the animal was carefully watched. The heart rate was taken every ten minutes until the greatest drop had been recorded and the heart showed signs of returning to normal.

1. The first series of dogs received no ether. (See Table I.)

2. The second series of dogs were anesthetized and then digitalis was administered. The heart rate was taken before anesthesia, during anesthesia, and during anesthesia with digitalis. (See Table II.)

3. The third series of dogs were given digitalis first and then anesthetized with ether. The heart rate was taken before anesthesia, after the administration of digitalis, and during digitalis action and anesthesia. (See Table III.)

TABLE I.

Weight in kilos.	Dose in cc. of digitalis.	Dose per kilo.	Normal heart rate.	Digitalis heart rate.	Slowing of heart as compared with normal.	Toxic symptoms.
15.9	0.318	0.02	121	100	21	None
21.8	0.438	0.02	124	100	24	"
26.8	0.536	0.02	96	76	20	"
10.7	0.214	0.02	120	88	32	"
9.3	0.186	0.02	108	84	24	"
9.8	0.196	0.02	115	93	22	"
14.5	0.29	0.02	130	98	32	"
17.5	0.35	0.02	122	96	26	"
10.0	0.2	0.02	98	82	16	"
10.94	0.208	0.02	137	114	23	"
17.3	0.356	0.02	112	90	22	"
23.6	0.462	0.02	102	87	15	"
5.8	0.116	0.02	118	90	28	"
14.0	0.28	0.02	104	84	20	"
18.8	0.376	0.02	118	90	28	"

TABLE II.

Weight in kilos.	Dose in cc. of digitalis.	Dose per kilo.	Normal heart rate.	Heart rate under anesthesia.	Heart rate under ether and digitalis.	Slowing of heart as compared with normal.	Toxic symptoms.
14.0	0.28	0.02	107	169	132	None	Incr. rate of respiration
13.3	0.25	0.018	98	176	150	None	None
8.7	0.174	0.02	108	150	140	None	Diarrhea
5.1	0.102	0.02	145	166.2	136	9 Beats	None
10.94	0.208	0.02	138	180	150	None	Vomiting
21.8	0.438	0.02	126	178	148	None	Incr. rate of respiration
17.3	0.34	0.02	118	156	122	None	Nausea and vomiting
14.0	0.28	0.02	104	172	141	None	Incr. rate of respiration
23.0	0.46	0.02	106	182	140	None	Vomiting
16.0	0.32	0.02	112	170	132	None	Nausea and vomiting
10.3	0.206	0.02	140	181	152	None	None
9.8	0.196	0.02	118	156	117	1 Beat	None
9.3	0.186	0.02	104	148	120	None	Vomiting

TABLE III.

Weight in kilos.	Dose in cc. of digitalis.	Dose per kilo.	Normal heart rate.	Digitalis heart rate.	Digitalis and ether heart rate.	Slowing of heart as compared with normal.	Toxic symptoms.
10.94	0.208	0.02	137	114	140	None	None
21.8	0.438	0.02	122	98	134	None	Vomiting
14.0	0.28	0.02	112	90	128	None	None
18.5	0.19	0.02	108	80	112	None	None
16.3	0.326	0.02	119	90	115	4 Beats	None
8.4	0.168	0.02	120	92	131	None	Vomiting
6.8	0.136	0.02	140	116	139	1 Beat	None
13.6	0.272	0.02	130	110	138	None	Vomiting
12.2	0.24	0.02	102	84	121	None	Diarrhea
10.1	0.202	0.02	126	98	132	None	None
23.4	0.468	0.02	120	96	118	2 Beats	None
8.4	0.168	0.02	116	93	126	None	Vomiting
13.1	0.262	0.02	102	80	112	None	None

DISCUSSION.

From the foregoing experiments it was found that doses of digitalis when given to the normal animals produced no toxic effects, but when the same doses were given to the same animals under anesthesia, toxic symptoms appeared.

The dose necessary to produce toxic effects or a certain percentage drop in heart rate in a dog depends upon the normality of the cardiac mechanism upon which the drug is to act. Therefore, if the drug is to be standardized, it is to be done on a normal animal, as a wide difference in the preparations standardized on an anesthetized animal may occur. From a clinical standpoint, it is important to decrease the dose of digitalis administration before operation under ether as the anesthesia increases the toxicity of the digitalis.

From the experiments carried out on dogs, one would be led to believe that digitalis as a heart inhibitory stimulant is of no value during active anesthesia.

Note.—The tincture of digitalis used in these experiments was standardized by the following method, which briefly consists of the intravenous injection of the drug into a normal dog without anesthesia. The heart rate is counted before and after the injection of the drug and the slowing of the heart rate is taken as a measure of the activity of the drug. If the preparation be of standard strength, 0.02 cc. of the tincture per kilo weight of the dog will reduce the heart rate 20 per cent in from thirty to sixty minutes.

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PRODUCTION OF OIL OF PEPPERMINT.*

BY G. A. RUSSELL.[1]

INTRODUCTION.

The production of oil of peppermint is not confined to any one particular country. Its production is, however, fairly well confined to the Northern Hemisphere. As far as I am aware, no peppermint is produced commercially south of the equator. The chief countries of production are the United States, England, France and Italy. Some oil is produced in Germany and Russia and small plantings are to be found in practically all countries. Australia recently has been experimenting somewhat extensively and intensively in the production of oil of peppermint and the published reports indicate very favorable results.

It must be understood that in this discussion reference is made only to the oil of peppermint from *Mentha piperita*. The so-called Japanese peppermint oil is obtained from *Mentha arvensis;* and is recognized in this country under the common name "Corn Mint Oil." Its production runs into hundreds of thousands of pounds and is of sufficient interest to warrant special attention. This paper does not consider Japanese corn mint oil but is confined to peppermint oil as we know and understand it.

The botany of peppermint is somewhat complicated. Suffice it to state here that the main source of the oil is from *Mentha piperita* var. *officinalis*. Of this species there are many modifications, chief of which are the so-called "black" and "white" mints. The "black" mint is the form most extensively cultivated since it yields more oil than the "white" although the quality is not so good.

The world production of peppermint oil, not including Japan, is in the neighborhood of 500,000 to 600,000 pounds, of which the United States produces the major portion. Next to Japan we are the largest producers of mint oil of any description; this paper is confined to the home activities.

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