(8) Chapman, "Comparative Studies of Propylene, Ethylene, Nitrous Oxide and Ether," *J. Pharmacol.*, Vol. XXVII, No. 2 (March 1926).

ABSTRACT OF DISCUSSION.

In reply to questions, the author stated that studies are under way for the estimation of propylene and various gases in the blood. He had experienced no nausea from administration of propylene. He had with him about 50 electro-cardiographic tracings.

THE INFLUENCE OF DIGITALIS ON THE RESISTANCE OF GUINEA-PIGS TO POISONING BY DIPHTHERIA TOXIN.*

BY CHARLES C. HASKELL.

It has been stated that digitalis is contraindicated in diphtheria and other infections. In the experiments reported on, diphtheria was selected for the tests and it was found that the administration of tincture of digitalis, apparently, does not hasten the death of guinea-pigs that were coincidentally given a dose of diphtheria toxin.

The question of employment of digitalis in the treatment of the acute involvement of the heart which occurs in the course of certain infectious diseases is a cause of dispute among clinicians. A certain number contend that the drug is indicated here; others believe that, instead of being beneficial, in such cases it actually does harm. The discussion has been waged especially in regard to pneumonia, due either to infection with the pneumococcus or to other organisms; but, unfortunately, no positive evidence has been presented in support of either view as to the rôle of the drug in these conditions, although Jamieson has shown that the resistance of cats suffering from experimental pneumonia does not seem to be lowered to the toxic action of ouabain.

In 1919, Bush reported experiments which seemed to show that poisoning by diphtheria toxin increased the susceptibility of frogs and of dogs to the toxic action of digitalis. Two years later, McCulloch pointed out that the changes in the human electrocardiogram encountered in clinical diphtheria strongly resembled the changes produced by the toxic action of digitalis. On the basis of this observation, he contended that digitalis should never be administered to patients suffering from diphtheria.

As a matter of fact, it is rarely, if ever, that the administration of digitalis clinically in diphtheria is considered. However, if it could be clearly demonstrated that the drug acted deleteriously in this form of intoxication, it would suggest the possibility, at least, that it would have an unfavorable influence in those bacterial infections where its use is recommended by competent authorities. Diphtheria toxin is easily administered to animals and its potency is relatively constant from day to day; in these respects, it is decidedly superior to bacterial cultures, where exact dosage is difficult and where the virulence decreases rapidly under conditions of artificial cultivation.

In Bush's experiments, conditions quite unlike those existing clinically were present. His animals were given a single large dose of the toxin and, after 24 or

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* Scientific Section, A. PH. A., Philadelphia meeting, 1926.

48 hours, their reaction to toxic doses of digitalis was determined. McCulloch's observations are far from convincing: the mere fact that poisonous doses of digitalis produce electrocardiographic changes similar to those seen in clinical diphtheria does not prove that moderate doses of the drug will exert an unfavorable influence on the course of the disease. Because of these considerations, the attempt was made to ascertain whether single, large, non-fatal doses of the tincture of digitalis would affect the resistance of guinea-pigs to poisoning by diphtheria toxin.

The toxin used in these experiments was furnished by Parke, Davis and Co., and it is with pleasure that acknowledgment is made of the obligation to this firm for their courteous coöperation. The experiments here reported were carried out during the months of December 1924, and January, February and March 1925; it is possible that the seasonal variations in the resistance of the animals was manifested, but this was negatived by the fact that each series consisted of an equal number of digitalized and control animals. The dose of the toxin varied: in the earlier experiments, large amounts were used; later on, barely the M. L. D.

The tincture employed was percolated in our laboratory in 1920 from leaf grown in the vicinity of Richmond by J. W. Wilber. The question of dosage for the tincture was important; it was desirable to administer a large dose, comparable to that used in accordance with the Eggleston method of dosage; but it was equally as important to avoid using an amount of the tincture which alone might cause death. To be able to select what was considered an appropriate dose, the tincture was tested on guinea-pigs, in order to determine its toxicity. For this purpose a small portion was evaporated over a water-bath to a condition of semi-solidity; it was then suspended in a convenient volume of hot isotonic saline; usually equivalent to twice or thrice the original volume of the tincture. After cooling, different amounts of this suspension were injected subcutaneously into the guinea-pigs, and the animals kept under observation for 24 hours. In December 1924 the M. L. D. for the tincture, determined in this way, appeared to be in the neighborhood of 0.0025 cc. per Gm. body weight. This is evident from Table I.

TABLE I.—TOXICITY OF TR. 1920-W FOR GUINEA-PIGS.

Weight in Gm.	Dose of suspension, cc. × Gm.	Result.	Weight in Gm.	Dose of suspension, cc. × Gm.	Result.
370	0.0015	Survived	345	0.0022	Died
440	0.0015	Survived	215	0.0024	Survived
440	0.0020	Survived	260	0.0024	Died
250	0.0020	Survived	220	0.0025	Died
300	0.0020	Died	465	0.0030	Died
285	0.0022	Survived	335	0.0030	Died
260	0.0022	Survived	210	0.0030	Died

For the first series of animals, the dose of toxin administered subcutaneously was 0.00007 cc. per Gm. body weight. Subsequent tests indicated that this was about three times the M. L. D. The dose of the suspension of tincture employed was 0.002 cc. per Gm. body weight. Six guinea-pigs were included in this series; three receiving digitalis, three serving as controls. The results obtained are given in Table II.

TABLE II.—INFLUENCE OF DIGITALIS ON RESISTANCE OF GUINEA-PIGS TO DIPHTHERIA TOXIN.

Weight in Gm.	Dose of toxin, cc. × Gm.	Dose of digitalis suspension, cc. × Gm.	Duration of life.
265	0.00007	0	8 days
275	0.00007	0	2 days
250	0.00007	0	5 days
260	0.00007	0.002	3 days
220	0.00007	0.002	2 days
240	0.00007	0.002	2 days

Average duration of life:
Controls, 5 days. Digitalized, 2.33 days.

It is obvious from an inspection of Table I that the amount of the digitalis suspension is near to the fatal dose; certainly, it is far in excess of any dose of tincture of digitalis that would ever be employed clinically, when considered on the basis of body weight. With such a dose of digitalis, it seems from the results presented in Table II that the resistance of the animals is reduced.

In the next series, 8 guinea-pigs were used. The dose of the toxin was reduced to 0.000065 cc. per Gm. body weight; and that of the digitalis suspension to 0.0005 cc. per Gm. body weight; this latter constituting about 20% of the average fatal dose. The results are given in Table III.

TABLE III.—INFLUENCE OF DIGITALIS ON RESISTANCE OF GUINEA-PIGS TO DIPHTHERIA TOXIN.

Weight in Gm.	Dose of toxin, cc. × Gm.	Dose of digitalis suspension, cc. × Gm.	Duration of life.
240	0.000065	0	2 days
220	0.000065	0	4 days
250	0.000065	0	6 days
235	0.000065	0	4 days
200	0.000065	0.0005	4 days
190	0.000065	0.0005	6 days
190	0.000065	0.0005	3 days
200	0.000065	0.0005	2 days

Average duration of life:
Controls, 4.0 days. Digitalized, 3.75 days.

Here the influence of the digitalis is practically negligible; the average duration of life for the controls was 4 days; that for the digitalized animals, 3.75 days.

TABLE IV.—INFLUENCE OF DIGITALIS ON RESISTANCE OF GUINEA-PIGS TO DIPHTHERIA TOXIN.

Weight in Gm.	Dose of toxin, cc. × Gm.	Dose of digitalis suspension, cc. × Gm.	Duration of life.
310	0.00006	0	3 days
260	0.00006	0	3 days
360	0.00006	0	5 days
300	0.00006	0.001	3 days
230	0.00006	0.001	5 days
185	0.00006	0.001	8 days

Average duration of life:
Controls, 3.66. Digitalized, 5.30.

In the next experiments, the dose of the toxin was still further reduced, the amount injected being 0.00006 cc. per Gm. body weight while the dose of the digitalis suspension was increased to 0.001 cc. per Gm. body weight, this constituting approximately 40% of the M. L. D. for the suspension. Table IV contains the results.

Here, in spite of the fact that 40% of the average M. L. D. of the digitalis suspension was administered, the digitalized animals outlived the controls.

In the next series, the dose of the toxin was markedly reduced; only 0.00002 cc. per Gm. body weight being injected into the animals. On the other hand, the dose of the digitalis suspension was increased to almost the M. L. D., 0.002 cc. per Gm. body weight being injected immediately after the injection of the toxin. The results obtained are given in Table V.

TABLE V.—INFLUENCE OF DIGITALIS ON RESISTANCE OF GUINEA-PIGS TO DIPHTHERIA TOXIN.

Weight in Gm.	Dose of toxin, cc. × Gm.	Dose of digitalis suspension, cc. × Gm.	Duration of life.
205	0.00002	0	11 days
215	0.00002	0	Survived
215	0.00002	0	Survived
206	0.00002	0	Survived
215	0.00002	0.002	Survived
215	0.00002	0.002	1 day
206	0.00002	0.002	8 days
200	0.00002	0.002	1 day

Mortality: Controls, 25%. Digitalized, 75%.

A very definite effect was seen from the amount of the digitalis used in these experiments; the mortality among the controls was only 25% as compared with one of 75% for the digitalized animals. The possibility of the resistance of the animals to digitalis having decreased since the suspension had been originally assayed was considered; consequently, four normal guinea-pigs were given the dose of 0.002 cc. of the suspension per Gm. body weight; all survived, although they seemed to be critically ill at one time.

In the next series were eight pigs. The animals were given 0.000025 cc. of the toxin per Gm. body weight and 0.0015 cc. of the digitalis suspension per Gm. body weight. The results are presented in Table VI.

TABLE VI.—INFLUENCE OF DIGITALIS ON RESISTANCE OF GUINEA-PIGS TO DIPHTHERIA TOXIN.

Weight in Gm.	Dose of toxin, cc. × Gm.	Dose of digitalis suspension, cc. × Gm.	Duration of life.
330	0.000025	0	11 days
345	0.000025	0	11 days
345	0.000025	0	11 days
285	0.000025	0	12 days
310	0.000025	0.0015	Survived
295	0.000025	0.0015	8 days
270	0.000025	0.0015	Survived
250	0.000025	0.0015	4 days

Mortality: Controls, 100%. Digitalized, 50%.

With the reduction in the dose of the digitalis suspension, although the dose

of this preparation still amounted to some 60% of the average M. L. D., the digitalized pigs fared much better than did the controls.

DISCUSSION.

If one attempts to analyze the results of all the experiments, it immediately becomes obvious that the series falls into two groups; in one of these, as presented in Tables III, IV and VI, the digitalis certainly had no deleterious influence of any moment; in the other, as illustrated in Tables II and V, the drug seems to have lowered the resistance of the animals to the diphtheria poison. Furthermore, it is to be noted that where a harmful effect from the digitalis occurred, the dose of the drug was very large. As has already been pointed out, the average M. L. D. for this preparation of digitalis was placed at 0.0025 cc. per Gm. body weight, from tests carried out in December 1924. Although four animals survived a dose of 0.002 cc. per Gm. body weight in the latter part of January 1925, two succumbed from this dose in September of that year. It is obvious, therefore, that either we have to do with a seasonal variation of the animals in their resistance to digitalis poisoning or that a certain proportion will die from a dose some 20% below our accepted M. L. D. In view of the belief that the tincture of digitalis undergoes rapid deterioration, as determined by the guinea-pig method of assay, the behavior of this preparation is interesting. It is found that in some nine months its potency has not decreased in the slightest. It is possible, however, that the original potency of this tincture may have been considerably higher; unfortunately, no guinea-pig assay of it was made at the time of percolation in 1920.

Therapeutically, a single dose of digitalis of even half the lethal dose would never be intentionally employed clinically; with guinea-pigs, an amount of the drug as high as 60% of the M. L. D. certainly seems to have had no influence on the resistance to diphtheria toxin. It may be concluded just as definitely that no benefit was evident from the digitalis employed in the experiments here reported. It is true that the figures in Tables IV and VI suggest the contrary; in Table IV, the average duration of life for the controls was only 3.66 days as compared with 5.3 for the digitalized animals; while in Table VI, all of the controls succumbed, while only two of the digitalized animals died during the period of observation. The small number of animals used, however, prevents attaching importance to those instances; moreover, the duration of life for the two digitalized pigs in Series 6 where death did occur was only 6 days as compared with a duration of over 11 days for the controls. The following conclusions appear to be justified:

1. When single doses of a suspension made from a tincture of digitalis in the manner described are injected about the same time as the toxin, amounts as large as 60% of the M. L. D. do not appear to lower the resistance of these animals to poisoning by diphtheria toxin, so as either to cause death where recovery otherwise would have taken place or to hasten death as compared with the time in which it occurred in the case of the controls.

2. Moderately large, single doses of the digitalis suspension do not appear to have any favorable influence on the resistance of guinea-pigs to poisoning by diphtheria toxin.

3. A certain degree of synergism seems to exist between the diphtheria toxin and the digitalis: amounts of the suspension cause death of guinea-pigs poisoned with the diphtheria toxin while controls receiving this amount of the suspension usually recover.

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LAY CONCEPTIONS OF ANTISEPTICS.

In an address before the recent annual meeting of the American Drug Manufacturers' Association Dr. John S. Jamieson, former medical officer of the U. S. Bureau of Chemistry, said in part as follows:

"In order to ascertain, at least to some extent, what the general lay conception of the term antiseptic is, particularly when used in connection with products sold as, for instance, mouth washes, inquiry was made of a number of individuals making up what was considered to be a fairly representative cross section of everyday life; that is to say, ministers, lawyers, clerks, merchants, milliners, salespersons, railroad employees, school teachers, housewives and the like were interrogated. In no instance was a reply received referring in any way to inhibition; the consensus of the opinion elicited was that an antiseptic mouth wash freed the mouth of germs, killed germs or did away with germs. The impression conveyed by the word evidently involved the fuller and less technical significance of actual germicidal effect. Therefore, to the public an antiseptic product of the kind in question means one that is against sepsis, in that it prevents or does away with that condition to as great an extent as possible. In line, therefore, with court decisions that the wording on labels is to be given the meaning ordinarily conveyed by it to those to whom it is addressed, that is, to the lay public, or, colloquially, the man in the street, the Bureau believes that products used as mouth washes, sprays, gargles, douches and the like, which are in brief contact with the tissues and subject to immediate dilution by the secretions, should be designated antiseptic only if, when in the dilution mentioned in the directions, they are germicidal in a brief period of time. If the effect produced by such articles involved inhibition only, the action on microörganisms would be inconsequential, a false feeling of security would be induced, and possibly valuable time would be wasted in using a product which had no positive germicidal effect. As stated, this applies to mouth washes, gargles, douches and similar products. Preparations used as ointments, wet dressings, or applications which remain in contact with the tissues for a protracted period may properly be termed antiseptic if they are capable of preventing any development of bacteria.

INHIBITORY PREPARATIONS.

"It has been argued that use of products such as mouth washes and the like which inhibit, and do not destroy, germs is better for the individual, since a pronounced germicidal action may in some instances affect the cells of the mucous membrane with which the preparation is brought into contact. Under the provisions of the act, however, the Bureau is not concerned with the kind of ingredients used, provided the preparation is properly labeled as regards its germicidal