THE EFFECT OF RADIO VIBRATIONS ON SOME DRUGS.*

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INTRODUCTORY.

It is a matter of common knowledge that ultraviolet rays may profoundly affect various properties of chemicals and drugs. The writer has found, for instance, that exposure to ultraviolet radiation modifies the action of quinine and quinidine sulphates on rats (1). It is also well known that X-rays, radium and radium emanations may produce marked chemical reactions and modify the pharmacological properties of drugs. Thus the author has recently shown that both ordinary ultraviolet radiation and very short ultraviolet rays, designated as X-rays and radium emanations, modify the potency of digitalis tincture (2). Going to the other extreme of the spectrum, it is now known that infra-red radiations may also induce changes in chemicals; and even the rays of the visible spectrum of light, especially when polarized, have been shown by the writer and his co-workers to be capable of influencing the pharmacological properties of various chemical compounds and drugs (3). These facts prompted the undertaking of the present investigation.

Any one in the proximity of a modern radio with a loud speaker may observe that the sounds emitted by the apparatus, especially those of the lower register, cause audible vibrations of china, picture frames and other light articles in the same room. Indeed, these vibrations produced by the loud speaker may actually be transmitted to the floor and felt by persons occupying chairs in the room. The question arises: Can such vibrations induce or hasten reactions in any substance which may be detected by some chemical, physical or biological methods? Inquiry into such a subject may prove to be of practical importance because radios are common adjuncts or articles of furniture in many households of the present day.

The following experiments, undertaken as a preliminary investigation of this problem, were primarily of a practical nature. No attempt was made to analyze or determine exactly what sort of vibrations produced by the radio—whether supersonic waves, ordinary audible sound waves or mechanical vibrations set up by the instrument—were responsible for the results reported here. Such an analysis is reserved for a future detailed study.

METHODS OF EXPERIMENTATION.

The experiments were made with a so-called "baby grand" radio set (one of the best known, latest models), placed on a small wooden table resting on the wood floor. Several chemicals or drugs in ordinary glass test-tubes, clamped to an iron stand on the floor, were placed as closely as possible to the instrument. Care was taken to protect the solutions from light, both direct and indirect, by means of black paper; and control solutions of exactly the same kind were placed in other test-tubes wrapped in cotton wool and inclosed in a large mailing tube left in the same room with the radio. Thus light was eliminated and the temperature of both specimens properly controlled. Periods of exposure to the radio vibrations lasted

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from three to six hours, and sometimes longer. The musical programs used for such experiments included rendition from both wind and stringed instruments and vocal recitals. Whenever possible, symphonic music was the source of sound vibrations.

Five different chemicals or drugs were chosen for study in this research: tincture of digitalis, aqueous solution of Mercurochrome, solutions of physostigmine or eserine salts, solutions of cocaine hydrochloride and benzaldehyde. These widely different drugs were purposely selected in order to take advantage of various methods of detecting possible differences in their chemical composition, on the one hand, and phsyiological action, on the other. The methods of study in some cases were physical, for example, colorimetric comparison or hydrogen-ion determination by means of an electric potentiometer; in other cases, purely chemical quantitative methods were employed, for example, determination of metallic mercury; and special pharmacological methods were used in case of digitalis and cocaine because, as is well known, certain changes in chemical constitution can be more readily detected by extremely sensitive biological tests than by the methods of physics and chemistry (4).

DIGITALIS.

Digitalis was the first drug chosen for experimentation because of its importance in medicine and because, as is well known, all its preparations, including the tincture, undergo a change in potency on standing. Since such changes cannot be followed satisfactorily by any chemical test and the potency of digitalis preparations must be studied by biological methods, numerous experiments were made with various tinctures exposed to radio vibrations. Each tincture employed was divided into two portions, one used as a control and the other exposed to radio vibrations. The control was always kept in the same room with the radio to eliminate any difference that might be ascribed to variations in temperature. After exposure of the one portion to radio vibrations, both specimens were assayed or compared pharmacologically. The methods principally used were the cat method of Hatcher and Brodie, as modified by Rowntree and Macht (5), and the phytopharmacological test described by Macht and Krantz (6). In addition, comparative tests with the specimens were made on goldfish (*Carassius auratus*) and on leeches (*Hirudo medicinalis*).

Two series of cat experiments were performed. In one series, the usual method with intact vagi nerves was employed. In another series, assays were made on animals with both vagi cut because the author has found that when digitalis preparations are assayed on vagotomized cats, the results obtained are not only more uniform but also indicate a greater toxicity of the drug (7). Table I shows the results obtained. It will be noted that in both series there was a difference of

TABLE I.—DIGITALIS ASSAY ON CATS.

Specimen.	Number of Cats.	Vagi.	Minimum Lethal Dose (Average).
Normal or control	7	Intact	10.1 cc. of 1:10 solution
Exposed to radio vibrations	7	Intact	10.6 cc. of 1:10 solution
Normal or control	8	Cut	7.4 cc. of 1:10 solution
Exposed to radio vibrations	8	Cut	7.9 cc. of 1:10 solution

0.5 cc. in the minimal lethal dose between the control and the specimen exposed to

radio vibrations. Phytopharmacological comparisons revealed a much greater difference between the "radio" and control specimens. The results obtained in sixteen experiments are exhibited in Table II.

TABLE II.—PHYTOPHARMACOLOGICAL EXPERIMENTS WITH DIGITALIS, 1%, ON LUPINUS ALBUS.

Number.	Experiment.	Phytotoxic Index of Normal or room control.	Phytotoxic Index of Specimen exposed to radiations.
1	December 14	76%	83%
2	December 15	52%	62%
3	December 21	56%	69%
4	December 22	44%	57%
5	June 8	42%	54%
6	June 9	64%	59%
7	June 13	50%	57%
8	July 5	61%	76%
9	July 6	57%	67%
10	July 11	58%	71%
11	July 18	50%	72%
12	July 20	58%	78%
13	August 29	50%	63%
14	September 1	76%	81%
15	September 5	64%	92%
16	September 22	51%	66%

Each specimen of tincture was tested on eight or ten seedlings of *Lupinus albus* suspended in a one per cent solution of the tincture in plant-physiological saline; and the index of growth, or phytotoxic index, as compared with that of seedlings in normal physiological solution, is expressed in percentages. It will be noted that there was usually a difference of 10 per cent, and often more, between the controls and the treated specimens.

In addition to the cat and plant experiments, comparative tests were made on goldfish with a 2 per cent solution of the tinctures. Here again, a difference in toxicity was noted between the "radio" and control specimens, as shown by the following protocol:

ASSAY ON CARASSIUS AURATUS.

Specimen of Digitalis Tincture, 2%.	Fish Paralyzed in
Normal or control	6 minutes
Exposed to radio vibrations	10 minutes

In connection with pharmacological studies made on leeches in this laboratory, the author had occasion to test the toxicity of digitalis on these interesting animals. It was found that from 2 to 4 per cent solutions of digitalis tincture produced gradual paralysis of these worms. By employing this method in the present investigation, the author found again a definite difference between the "radio" and control specimens of tincture of digitalis, as illustrated by the following protocol:

ASSAY ON HIRUDO MEDICINALIS.

Specimen of Digitalis Tincture, 4%.	Leech Paralyzed in
Normal or control	22 minutes
Exposed to radio vibrations	30 minutes

MERCUROCHROME.

One of the valuable and striking properties of Mercurochrome, or dibrom-oxy-mercuri-fluorescein, is its great chemical stability. Solutions of this antiseptic, allowed to stand in the laboratory for months and even years, undergo no decomposition (8). It has been found that even exposure to the ultraviolet rays of a mercury lamp produces no breakdown of this compound (9). When mercury solutions are mixed with strong solutions of dextrose, however, the compound undergoes a slowly progressive reduction with precipitation of metallic mercury. A mixture of the drug with dextrose or glucose forms a less toxic dose for intravenous injection in animals, including man, than an aqueous solution of Mercurochrome but, because of the slow reducing process, it is advisable to prepare such mixtures immediately before their clinical administration to patients (10). Because of this slow chemical reduction brought about by the addition of large quantities of glucose to aqueous Mercurochrome solutions, such mixtures were selected for the study of the effects of radio vibrations. A solution of 5 per cent Mercurochrome, containing from 5 to 10 per cent of glucose, was prepared and divided into two parts. One fraction was exposed to the vibrations of the radio, while the other was used as a control. After the former had been exposed for a number of hours, the specimens were compared in regard to their chemical composition and also in respect to their pharmacological properties. The results obtained were very striking.

A quantitative determination of the rapidity of reduction of Mercurochrome was made by measuring the amount of metallic mercury precipitated from a given quantity of the solution. The author is indebted to Dr. Wilton C. Harden for the chemical analyses made in connection with this work. The subjoined protocol strikingly illustrates the results obtained. Three test-tubes, each containing 10 cc. of a 5 per cent solution of Mercurochrome with 10 per cent of glucose, were exposed to radio vibrations; and three others, filled with the same solution, were used as controls. The amount of metallic mercury precipitated in each of the test-tubes during six hours' exposure is shown in the protocol. It will be noted that a larger amount of metallic mercury was precipitated in all the exposed specimens than in the three controls. The results clearly indicate an acceleration of the reduction process in the specimens exposed to radio vibrations.

TABLE III.—EXPERIMENTS WITH MERCUROCHROME—QUANTITATIVE DETERMINATION OF METALLIC MERCURY. (February 17, 1932.)

Control Fraction.	Grams of Metallic Mercury in 10 cc. of Solution.	Fraction Exposed to Radio Vibrations.	Grams of Metallic Mercury in 10 cc. of Solution.
No. 1	0.0533	No. 1	0.0749
No. 2	0.0551	No. 2	0.0727
No. 3	0.0566	No. 3	0.0744

The two series of specimens described above were centrifugalized and filtered. The filtrates were then tested pharmacologically for their effect on growth of Lupinus seedlings as the writer has found this method useful in comparing the toxicity of various specimens of Mercurochrome (11). The phytopharmacological test also revealed a distinct difference between the exposed specimens and the controls, which is illustrated by the following protocol. Inasmuch as no mercury

was precipitated in the fraction exposed to radio vibrations, the supernatant fluid of this specimen was found to be less toxic than that of the control solution.

EXPERIMENT. (February 17, 1932).

Supernatant fluid of fraction exposed to radio vibrations, tested on *Lupinus albus* seedlings in a 1:5000 solution, gives a phytotoxic index of 58 per cent.

Control gives phytotoxic index of 40 per cent.

BENZALDEHYDE.

A fresh specimen of chemically pure benzaldehyde was used for further study of radio vibrations. It is well known that benzaldehyde, on exposure to air, slowly undergoes oxidation with the formation of benzoic acid. A fresh specimen of benzaldehyde was divided into two parts. One portion was exposed to radio vibrations, while the other was kept as a control. After exposure of one fraction for a number of hours, the two specimens were titrated by Dr. W. C. Harden to determine the amount of oxidation which had taken place in each. It was discovered that the specimen which had been exposed to radio vibrations required more sodium hydroxide to neutralize its acidity (in other words, a larger quantity of benzoic acid was found therein) than did the control. The following protocol illustrates these findings.

EXPERIMENT WITH BENZALDEHYDE. (April 27, 1932.)

Control Specimen:	*Specimen Exposed to Radio Vibrations:*
3.0 cc. of benzaldehyde requires 72.6 cc. of *N*/50 sodium hydroxide to be neutralized, which corresponds to 5.6 per cent of benzoic acid, $C_6H_5.OH$.	3.0 cc. of benzaldehyde requires 81.0 cc. of *N*/50 sodium hydroxide to be neutralized, which corresponds to 6.2 per cent of benzoic acid, $C_6H_5.OH$.

PHYSOSTIGMINE.

It is well known that solutions of physostigmine or eserine salts undergo a gradual change on standing even in the dark. They become pink or red in color through formation of a substance known as Rubreserin. The writer prepared solutions of eserine sulphate, 1:1000, in water and exposed them to radio vibrations. After from five to six hours' exposure, the color intensity of the specimen was compared with that of the control. It was found that the former had a distinctly deeper red color, indicating more rapid decomposition of the drug. The two solutions were then compared in respect to their myotic action on the pupil of the cat's eye. It was found that the darker solution (the one exposed to radio vibrations) was less effective in producing myosis than the control. Similar differences in pharmacological action were noted when the two specimens were compared on surviving intestinal segments of the cat.

COCAINE.

Cocaine and its salts are admirably adapted for the study of their keeping qualities or stability because their chemical structure and decomposition products are well known. The cocaine molecule is broken down by hydrolysis into three components, methyl alcohol, benzoic acid and a nitrogenous base known as ecgonin. These compounds do not exhibit the pharmacological properties of the cocaine

molecule in any way, neither do physical mixtures of the three produce the same physiological results effected by their chemical combination in the form of the cocaine molecule, with respect to influence on the nervous system (12) or muscular activity (13).

Solutions of cocaine hydrochloride, 0.2 and 0.1 per cent, were employed in the present study on the effect of radio vibrations. These were exposed according to the procedure described above and compared in various ways with the controls. Comparative tests were made in regard to the local anesthetic properties of the two solutions for frog's skin and the rabbit's eye. A more quantitative comparison of the two specimens was also made by taking advantage of the peculiar phytopharmacological properties of cocaine and its products of decomposition. Macht and Livingston (14) have demonstrated that, while cocaine itself is not very poisonous, some of its decomposition products, and more particularly benzoic acid, are very toxic for living plant protoplasm. It was found, for instance, that sodium benzoate, even in concentrations of 0.004 per cent, produces a marked inhibition in the growth of *Lupinus albus* seedlings. Specimens of cocaine hydrochloride, which had been exposed to radio vibrations, were compared with controls in regard to this effect on the growth of *Lupinus albus*. It was found that the exposed specimens were more toxic for plants than the control solutions. This indicated a greater decomposition in the former than in the latter, the increased toxicity being due to the presence of a larger amount of benzoic acid or benzoate in the exposed specimen as a result of decomposition. The following protocol illustrates these phytopharmacological findings.

TABLE IV.—EFFECT OF SOLUTIONS OF COCAINE HYDROCHLORIDE ON GROWTH OF LUPINUS ALBUS.

Experiment of.	Concentration.	Phytotoxic Index of Control specimen.	Phytotoxic Index of Specimen exposed to radio vibrations.
December 15, 1931	1:2000	81%	70%
December 21, 1931	1:1000	91%	64%
December 22, 1931	1:2000	55%	50%
March 4, 1932	1:2000	92%	73%

Zoöpharmacological experiments also proved that the control solutions of the cocaine hydrochloride were more anesthetic for frog's skin and for the conjunctiva of the rabbit's eye than those exposed to radio vibrations, thus corroborating the evidence already adduced as to the greater decomposition of the latter. Finally, a hydrogen-ion determination of the two solutions was made. It was found that the two specimens no longer possessed the same hydrogen-ion concentration. Thus the control solution gave a p_H of 4.4 while that exposed to radio vibrations gave a p_H of 3.8. This difference in the hydrogen-ion concentration again corroborated the evidence given by the other tests in regard to the more rapid decomposition of the exposed specimen.

COMMENT.

In 1927 Wood and Loomis described some physical and biological effects of high frequency sound waves of great intensity (15). These investigators studied sound waves of high frequency and great intensity, which were generated in an oil-bath by a piezo-electric oscillator of quartz, operated at 50,000 volts and vi-

brating 300,000 times a second: They noted certain heat and searing effects and liberation of gases dissolved in water; also destructive effects on spirogyra, small fishes and frogs. Harvey and Loomis, in a later work (16), described the effects of high frequency sound waves of small intensity in relation to their biological effects on cells of Elodea and Nitella. Further work concerning the effects of high frequency sound waves on protoplasm was carried on by Schmitt, Olson and Johnson (17), who developed a technique for supersonic micro-manipulation. More recently, Hsien Wu and Szu-Chih Liu reported further experiments concerning the effect of supersonic waves on protoplasm (18). A valuable contribution concerning the purely chemical effects of high frequency sound waves first described by Wood and Loomis was published by Richards and Loomis (19). They demonstrated that intense high frequency compressional waves produced certain chemical effects, "especially discharging metastable systems of great sensibility." They found that such waves expel gases from liquids and accelerate certain well-known chemical reactions. So far as the writer has been able to learn, no experiments have been recorded regarding the effects of high frequency and supersonic sound waves on drugs; certainly the effects of vibrations or oscillations emitted by the radio on the pharmacological properties of medicinal agents have not been described before, and the present communication is the first one of that type. The results obtained by the writer with solutions of the five drugs studied by various physical, chemical and biological methods are so clear-cut as to establish beyond doubt that the sounds or vibrations produced by the radio with a powerful loud speaker may accelerate chemical changes in solutions of drugs which are measurable by physicochemical or pharmacological tests. No experiments have yet been made with drugs in solid form. The author wishes to reiterate that so far he has not determined which vibrations or waves—whether supersonic or audible sound waves or mechanical vibrations—are responsible for these changes. Such an analysis is a fascinating subject for further research. The present findings, however, are obviously of practical importance in connection with the keeping qualities of drugs. It is hoped that the present study will stimulate further investigation in this field.

SUMMARY.

1. Solutions of five different drugs were exposed to the sounds or vibrations of a radio by being placed in close proximity to the loud speaker.

2. After exposure to such vibrations for several hours, these drugs were compared with control specimens of the same solutions by means of chemical, physical and biological tests.

3. It was found that the specimens exposed to radio vibrations had undergone greater chemical change than the control solutions.

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STUDIES ON THE PREPARATION, TOXICITY AND ABSORPTION OF BISMUTH COMPOUNDS. IV. BISMUTH COMPOUNDS OF THIOGLYCOLLIC ACID.*

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Very little information is available in the literature concerning the toxicity and absorption of sodium bismuth thioglycollates. Harden and Dunning (1) have described the preparation of bismuth thioglycollamide but no data has been published on its toxicity and absorption. A little clinical data is available concerning a market preparation of sodium bismuth thioglycollate but no detailed comparison of the biological characteristics of this and other bismuth compounds has been made. It was the purpose of this investigation to compare bismuth thioglycollates and other bismuth compounds already discussed in previous publications as to their relative toxicity and absorption, as well as to describe their preparation.

Three bismuth derivatives of thioglycollic acid have been prepared: (1) Sodium Bismuth Thioglycollate; (2) Ethyl Thioglycollate; and (3) Bismuth Thioglycollate Triamide.

Of the three bismuth compounds prepared, only two were subjected to biological tests. Both of these were examined as regards their toxicity and absorption in the same manner as those previously discussed. They were injected intramuscularly into albino rats. The absorption was studied by determining quantitatively the unabsorbed bismuth still remaining at the site of injection while the toxicity was estimated from the growth curves of the rats injected. The results obtained are given in the following table. Owing to the slight solubility of bismutho thioglycollamide in water it was necessary to inject it in glycerin solution.

Compound Injected.	Medium for Injection.	Dosage Injected— Mg. Bi/Kg. Body Weight.	Approximate Maximum Tolerated Dose— Mg./Kg. Body Weight.	Per Cent Absorption.
Sodium bismuth thioglycollate	Water	15	Less than 30	38% in 27 days
Bismuth thioglycollamide	Glycerin	50	Less than 50	82% in 3 hours

These two compounds are both more toxic than the bismuth compounds of the fatty acids, the bismuth tartrates, and the iodobismuthates of quinine and

* Scientific Section, A. PH. A., Toronto meeting, 1932.