SCIENTIFIC SECTION

A SIMPLE METHOD OF STUDYING RESPIRATORY PHARMACODYNAMICS.

BY DAVID I. MACHT, M.D.

INTRODUCTORY.

The study of the respiratory function, as affected by drugs, is a very complicated subject. In order to ascertain completely the effect of any given chemical substance on the respiration, the action on various functions must be studied. A drug may affect the respiration indirectly through increasing or decreasing the *metabolism*. Again, it may exert its influence upon the respiratory function through its action on the *circulation*, especially through circulatory changes in the brain or spinal cord and also through peripheral vasodilatation and consequent loss of temperature. Also it may alter the general character of breathing by changes in the *mechanical conditions* within the chest or abdomen as, for instance, by its action on various viscera or on the thoracic or abdominal musculature. It may alter the respiration by its action on the *bronchi*, producing constriction or dilatation, thus altering the so-called "dead space" within the chest cavity, etc. In order to obtain information concerning the effects described above, studies have to be made in the laboratory upon the rate of respiration, the volume of air respired or total ventilation, the alveolar or true ventilation of the lungs, the direct effect on the respiratory center, direct effect on the bronchi, etc. A detailed discussion of all these factors is given by the author in a previous publication, dealing with the action of opium alkaloids, individually and in combination with each other, on the respiration.[1]

For a great many purposes, in connection with pharmacological studies on drugs, sufficient information in regard to effects on the respiratory function can be obtained by recording tracings produced by *movements of respired air* in and from the lungs, in various ways which may be found described in textbooks, on pharmacological technique. In the present paper, the author wishes to describe briefly a simple and very efficient method of recording such tracings which give a good idea as to the rate and depth of respiration, as well as its regularity in large animals, such as rabbits, cats and dogs. In reality, two different procedures are employed in such work, one method being utilized in intact animals, either with or without general anesthesia, depending on the drugs to be studied, the other being employed where a tracheotomy is demanded with the use of ether or other volatile anesthesic.

STUDIES ON INTACT ANIMALS.

In cases where a tracheotomy is resorted to, the following method is used to advantage. Very small metallic tubes or cannulæ, such as are manufactured by the Harvard Apparatus Company, under the name of "tracheal tubes" for

[1] Macht, *J. Pharmacol. & Exper. Therap.*, 7 (1915), 339–373.

small animals and are illustrated in Fig. 1 A, are employed, the size of the cannula being adapted to the size of the animal. Such a little tube is connected by means of soft rubber tubing to a Marey tambour for recording on a kymograph, while the bevelled open end of the tube is inserted into a nostril of the animal. The procedure is a painless one and can be employed in unanesthetized animals. In order to prevent reflex sneezing, however, induced by the insertion of the tube into the nostril, the nasal canal is first completely anesthetized by swabbing with pure benzyl alcohol which has been shown by the author to be a powerful local anesthetic.[1] When a rabbit or dog has been carefully trained to lie quietly on the table, a respiratory tracing obtained in this way can be very easily taken without administration of any anesthesia and the effect of various drugs can be conveniently studied by injecting intravenously or administration in other ways.

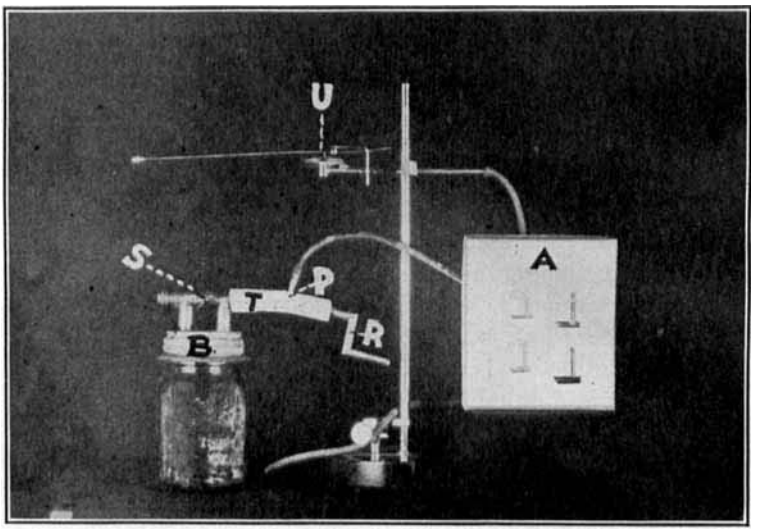

Fig. 1.—A, Small cannulae; B, Ether bottle; S, Stop-cock; T, Rubber joint; R, Tracheal tube; P, Insertion of respiratory cannula in rubber joint; U, Recording tambour.

The movements of the tambour record the rate of respiration, its depth and its rhythm, and also give a good idea as to any broncho-constrictor or broncho-dilator effect which may be produced by the administration of a pharmacological agent. Under general anesthesia with non-volatile anesthetics, such as urethane, paraldehyde, amytal, chlorbutanol, etc., such tracings through the nostrils can be obtained not only in rabbits and dogs but also in cats and, of course, in such cases, no local anesthetic is necessary.

STUDIES WITH TRACHEOTOMY.

In experiments where operative work is required and a volatile general anesthetic, such as ether, is to be employed and tracheotomy is performed, a different

[1] Macht, *J. Pharmacol. & Exper. Therap.*, 11 (1918), 263–279.

procedure must be followed, although the same small metallic tubes are still utilized. In Fig. 1 B is shown an ordinary ether bottle with a stop-cock (S) to regulate the relative volumes of air and ether inhaled. The ether bottle is connected by a piece of wide rubber tubing (T) to a regulation tracheal tube (R), which is inserted into the trachea of the completely anesthetized animal. At a point (P) in the rubber joint, connecting the large tracheal tube with the respiratory bottle, a small puncture hole is made through which the tiny metallic tube that was used for inserting into the nostril of the other animals, is inserted with its opening *toward* the animal. When the animal is breathing through the ether bottle, there is a sufficient amount of air diverted from the large tube (T) to produce oscillations of the tambour (U) and, in this way, a respiratory tracing can be obtained.

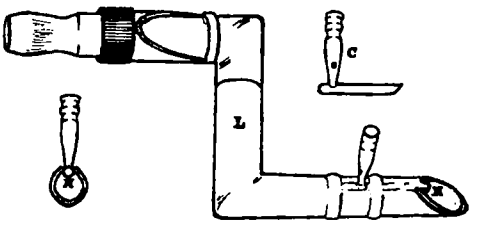

Fig. 2.—Tracheal tube with attachment for recording respiratory movements: L, Tracheal tube; C, Recording cannula; N, Front view, showing position of the aperture of the recording cannula in relation to that of the large tracheal tube.

In cases in which the excursions of the writing lever are too narrow, a still more efficient method can be employed, as illustrated in Fig. 2. Here a large tracheal tube (L) is shown, which is inserted into the trachea of the operated animal under general anesthesia. Near the proximate opening of this tube, a tiny "recording cannula" (C) has been soldered in such a way as to interfere to the least degree with the free passage of the inspired and expired air going through the ether bottle. The small recording cannula is fully sufficient, however, to give a wide excursion with the delicate Marey tambour for recording the rate and depth of the respiration, as part of the respired air moves back and forth through the small opening (N).

Fig. 3.—Respiratory tracing through nostril of rabbit, local anesthesia with benzyl alcohol. Sodium chloride, 0.9 per cent, produces no change in respiration. Pure mercurochrome, 10 mg., produces no change in respiration.

PRACTICAL ILLUSTRATION.

By the use of the methods described above, the author has obtained excellent tracings of great value in connection with studies of various drugs. In order to illustrate the results obtained, two kymographic records are produced in this place. In Fig. 3, a tracing was made of the respiratory movements of a rabbit by the use of the first method described, that is, by the insertion of a fine recording cannula in one of the nostrils previously anesthetized with benzyl alcohol. The

rabbit was lying very quietly on the table while the respiratory movements were recorded and Fig. 3 shows the results obtained by the injection of 0.5 cc. of a 2 per cent solution of pure oxymercuri-dibrom-fluorescein, or mercurochrome. This drug, as illustrated by the curve, does not influence the respiration at all and the effect is no different from that of physiological sodium chloride. Fig. 4 is a most interesting illustration of a tracing obtained in an anesthetized cat—by the second method described above. The cat was under ether anesthesia and the recording cannula was inserted close to the trachea. In this experiment, an examination was made of two fraudulent samples of a so-called antiseptic, obtained on the market. One of these was deliberately mislabeled as oxymercuri-dibrom-fluorescein, or "Mercurochrome, H. W. & D." The other bore on its label a name closely resembling that of mercurochrome. A chemical analysis

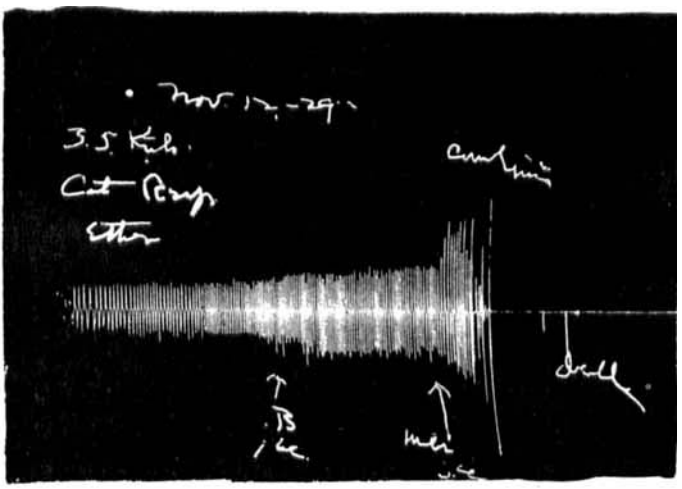

Fig. 4.—Cat, 3.5 kilo. Ether anesthesia. Respiratory tracing. At B, 1 cc. of fake "mercurochrome" No. 1 is injected, producing distinct stimulation of the respiration. At Mer., 2 cc. of fake "mercurochrome" No. 2 are injected, producing fleeting stimulation of respiration, followed by paralysis, convulsions and death.

of these samples by the chemists in the research laboratories of this institution revealed that both of them contained no mercurochrome at all and that both were a mixture of an inert dye with a most dangerous and violent inorganic poison, *cyanide of mercury*. Specimen No. 1 contained this poison in small quantity, which was not sufficient to produce death of the rabbit with the dose administered but gave a characteristic picture of cyanide action in higher animals. The second specimen contained so much mercuric cyanide that the respiratory function was quickly paralyzed, the animal went into convulsions and died within a few minutes. The effect of the cyanides on respiration is well known to all students of pharmacology. Minute doses of the cyanide ion (CN) produce a primary stimulation of the respiration, causing deeper breathing. Larger doses of the poison produce a fleeting primary stimulation quickly followed by *paralysis* of the respiratory

center, convulsions and death. In Fig. 4, at B, 1 cc. of the weaker mercuric cyanide counterfeit for mercurochrome was injected and, it will be noted, produced a distinct and marked stimulation of the respiration, indicated by the wider excursion of the tambour. At Mer., 2 cc. of the stronger mercuric cyanide antiseptic nostrum were injected. The respiration was stimulated for a second or two and was then paralyzed; the animal went into convulsions and died within three minutes. The amount of substance required to demonstrate the characteristic effect on the respiration in these experiments was a very small one. It may be well to add that administration of a small quantity of the second preparation to a rabbit by stomach also gave a characteristic picture of cyanide poisoning, 10 cc. producing death within ten minutes. Curiously enough, while both of the fake "mercurochrome" preparations contained a dangerous poison mixed with inert dye, a bacteriological examination of both specimens, made by Mr. Eric Drake, revealed that the first specimen was not antiseptic at all while the second was only very slightly so.

THE PHARMACOLOGY OF ERGOT WITH SPECIAL REFERENCE TO BIOLOGICAL ASSAY AND STANDARDIZATION.

(The bibliography will follow the last article of the series.)

PART IV. STUDY OF AQUEOUS EXTRACTS OF ERGOT.

BY MARVIN R. THOMPSON.[1]

The most widely used preparations of Ergot may be conveniently divided into two classes, depending upon the menstruum employed in the extraction processes, as follows: (*a*) Those involving the use of an aqueous menstruum for the extraction, such as Extractum Ergotæ Aquosum, N. F. (23), (commonly known as "Ergotin" or "Ergotine"), Extractum Ergotæ, and Extractum Ergotæ Liquidum of the B. P. (40); and (*b*) those involving the use of hydroalcoholic or acid-hydroalcoholic menstrua, as exemplified by Fluidextractum Ergotæ of the U. S. P. (24). Most proprietory preparations of Ergot also fall into one or the other of these two classes (see "New and Non-official Remedies," 1928 and 1929).

The aqueous preparations only are considered in this report. A study of the preparations of the second class will be reported in another paper of this series.

PREPARATION OF AQUEOUS EXTRACTS OF ERGOT.

The pharmaceutical procedure for the manufacture of Aqueous Extract of Ergot, N. F. (23) and that for the manufacture of Extract of Ergot and Liquid Extract of Ergot, B. P. (40) are essentially the same. In each case, the drug is extracted with an aqueous menstruum, the aqueous extract is concentrated at a moderate temperature, and supposedly inert material is precipitated by the addition of alcohol and filtered. The concentration of Liquid Extract of Ergot, B. P., is adjusted so that 1 cc. represents the water-soluble physiologically active principles of 1 gram of crude ergot. In the preparation of both the B. P. and N. F. semi-solid Extract of Ergot the aqueous extract must be further concentrated to a semi-solid or pilular consistence. Neither the N. F. nor the B. P. require the preparations to be standardized in any way.

The N. F. and B. P. differ slightly as to the aqueous menstruum employed in their preparations. The N. F. specifies chloroform water while the B. P. specifies water as the extraction men-

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