

SCIENTIFIC SECTION

A COMPARISON OF THE ACTION OF PITUITARY SOLUTION AND OF ERGOT ON THE ISOLATED HUMAN UTERUS.*

BY CHARLES C. HASKELL.

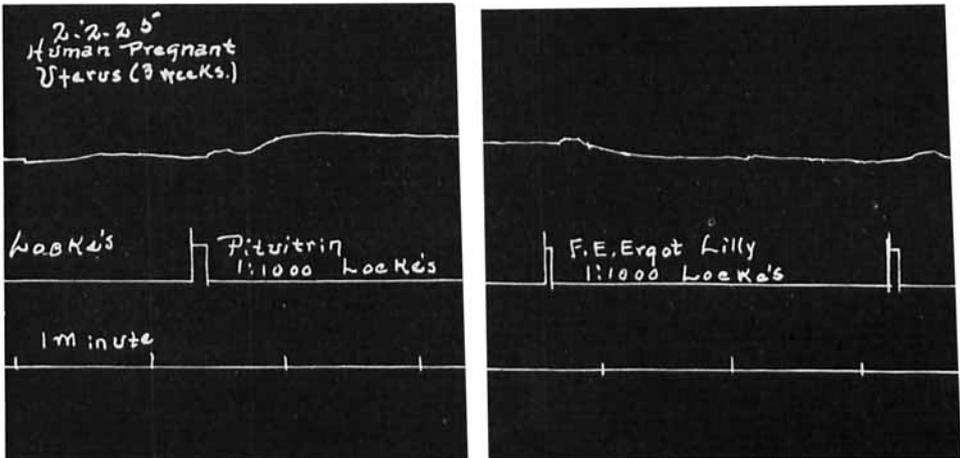
It is now universally conceded that the use of ergot in the early stages of labor is not permissible, because of the danger of uterine tetanus developing from the action of the drug. On the other hand, there are many obstetricians who contend that in pituitary solution we possess an agent that may be employed with impunity even in the first and second stages of labor, provided certain contra-indications are not present. The fact that pituitary solution has been used in thousands of obstetrical cases appears to support this view regarding its safety; but an examination of the literature shows that disaster occasionally accompanies the obstetrical use of this drug. Up to 1923, almost sixty cases of uterine rupture following the administration of pituitary solution had been reported; and this in spite of the singular hesitancy some obstetricians appear to feel in discussing the catastrophes which occur in their practice. Nor is uterine rupture the only evil consequence which has been ascribed to pituitary solution; of no less importance are the deleterious effects that may be exerted on the child; the increased intracranial pressure being responsible for cerebral hemorrhages, with the consequent death, paralyses, or mental impairment (1, 2).

It was not always felt that ergot was contra-indicated in the first and second stages of labor. In 1831, Ryan wrote of this drug: "In small quantities, it is a safe and valuable remedy, and has a specific effect on the uterus, exciting gradual but powerful contractions of that organ when the natural parturient action is diminished or has entirely ceased. It does not produce permanent contraction but merely renews the labor pains and augments their force . . . abridges human suffering . . . supersedes the use of instruments in many cases and it saves the attendant much anxiety and useless loss of time" (3). Because of disasters which have followed the use of ergot in the early stages of labor, this practice is now rightly condemned; in spite of a much larger number of disasters which have been reported as following such use of pituitary solution, there are many who would endorse Ryan's enthusiastic statements, were they made of pituitary solution.

In 1922, experiments were carried out in the Laboratory of Pharmacology of the Medical College of Va. and in the teaching hospitals of this institution with the object of determining the comparative activity of ergot and pituitary solution on the uterus (4). It was found that the uteri of cats and dogs responded much more readily to pituitary solution than to ergot and that tetanus was fully as apt to occur after pituitary solution as after ergot. Realizing the danger of administration of these drugs to pregnant women, only minimal doses were used, the contractions of the uterus being recorded by means of a mercury manometer connected with a Vorhees bag within that organ. With even the small doses administered, it was found that a persistent increase in tone occurred after pituitary solution, the

* The expenses of this investigation have been supported in part by a grant from the Research Fund of the AMERICAN PHARMACEUTICAL ASSOCIATION.

effect being equivalent to a true tetanus. It was felt that observations on the effect of the drugs on strips of excised human uteri would be of decided value; certain extraneous influences could be eliminated and the element of danger to the patient dispensed with. Gunn (5), Lieb (6), and Sun (7) have all observed the action of pituitary solution on strips of human uterus; Lieb has likewise experimented with ergot; none of these has carried out a definite comparison of the two drugs on the same specimen. Both Gunn and Sun observed tetanus following immersion of the strips in dilute pituitary solution, Sun especially having made a most exhaustive study of the activity of the strips under varying conditions. This author states: "When ergotol or quinine was added, no tetanic contractions were observed; but both of these drugs gave rise to rhythmic contractions which persisted for several hours . . . Upon the addition of pituitrin, however, an immediate response results, when contractions may be tetanic for a short time." These effects were produced on the lower uterine segment, which he normally finds



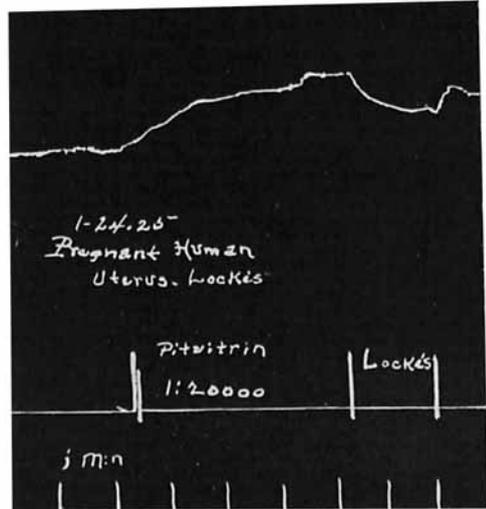
1. Human uterus: Third week of pregnancy: Fundic strip. At first signal, pituitary solution, 1 to 1000; tetanus persisted as long as allowed to remain in solution. At second signal, ergot, 1 to 1000, caused relaxation.

passive and quiescent. Lieb is inclined to the view that any reasonable concentration of pituitary solution does not cause tetanus; "in only one instance did pituitary cause even a transitory tetanus . . . The absence of tetanus has been repeatedly mentioned in the reports of the clinical use of pituitary." This statement is hard to reconcile with the only tracings which he publishes illustrating the action of pituitary; a concentration of pituitary, 1 to 50, causes a practically complete tetanus; while a concentration of 1 to 950 led to a marked and persistent increase of tone; fully equivalent to tetanus in its influence upon intrauterine pressure.

In the present study, experiments were carried out on both pregnant and non-pregnant uteri. The specimens were placed in Locke's solution shortly after removal from the patient; as soon as practicable, usually within an hour or two, small strips from the fundic portion of the uterus were immersed in warm (37° C.) oxygenated Locke's solution, and the contractions recorded in the usual manner. In

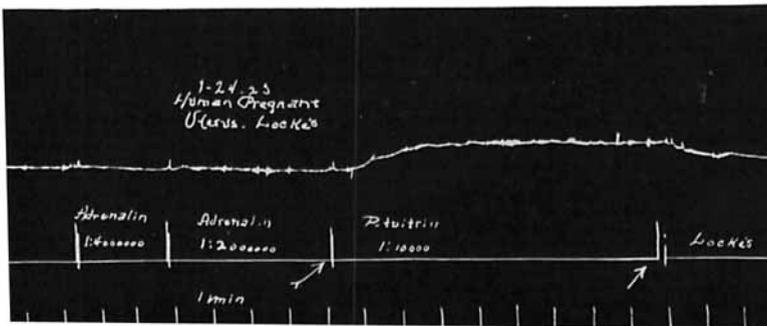
the earlier experiments, the mistake was made of adding the drug within a few minutes after setting up the apparatus; Sun has pointed out that at least two hours should elapse, this time being necessary for the establishment of stable condition of the strip. However, in the present experiments, this is unimportant, because the two drugs were compared under similar conditions.

Tracing No. 1 was the record of a strip from a uterus removed at about the third week of pregnancy because of pulmonary tuberculosis. The strip was immersed in the warm Locke's solution about ninety minutes after the uterus was removed; small, spontaneous contractions were immediately visible. The addition of pituitary solution to make a concentration of 1 to 1000 caused a persistent increase in tone, amounting to a true tetanus. In this experiment, fluidextract of ergot was added to make a concentration of 1 to 1000; a definite relaxation of the strip occurred. Lieb states that the alcohol in fluidextract of ergot is responsible for such an effect; this is possible, but the alcoholic concentration is certainly very low.



2. Pituitrin, 1 to 20,000. Pregnant uterus.

The second tracing was obtained from a strip removed at Caesarian section from a pregnant uterus at term. Pituitary solution, 1 to 2000, caused a much more pronounced response than was the case in the first tracing, the tetanus persisting as long as the strip was in the pituitary solution. The third tracing was obtained from a strip from the same specimen; after previous exposure to epine-



3. Pituitary solution, 1 to 10,000. Pregnant uterus.

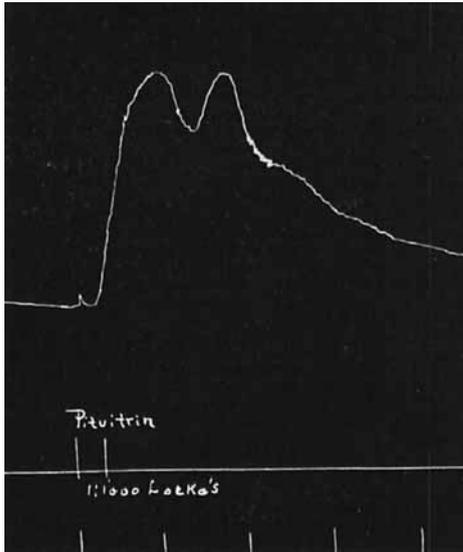
phrin, exposure of the strip to pituitary solution, 1 to 10,000, caused a marked response.

The fourth tracing was obtained from another specimen removed at Caesarian section from a full-term pregnancy. This strip was much more irritable than the

preceding; immersion in a solution of pituitary, 1 to 1000, for fifteen seconds caused the development of tetanus which persisted for almost ten minutes.

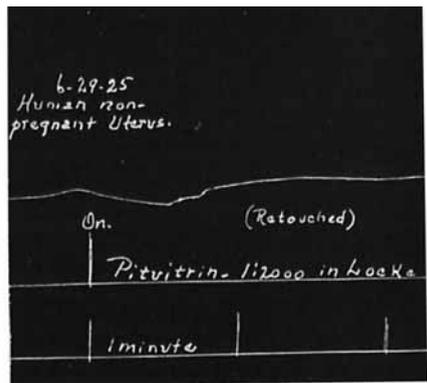
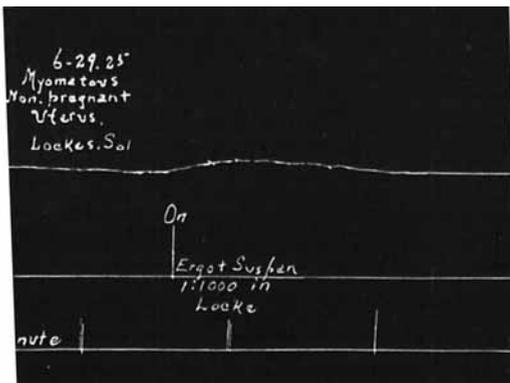
The fifth tracing was secured by recording the contractions of a strip removed from a non-pregnant uterus, showing extensive myomatous involvement. Even after two hours' immersion in the warm, oxygenated Locke's solution, this strip did not develop spontaneous contractions. A second sample of the fluid-extract of ergot was employed in this case; a measured amount of the fluid-extract was evaporated almost to dryness on a water-bath and the residue suspended in Locke's solution. It is apparent that this sample caused a single contraction of the strip, persisting about 80 seconds; pituitary solution, 1 to 2000, caused a tetanus which lasted for ten minutes, after which the solution was changed.

These results harmonize quite well with those of the previously reported experiments on the uteri of cats and dogs, indicating clearly that pituitary solution is even more prone than ergot to cause a persistent contraction of the uterus. Absolutely no basis could be found for the statement that low concentrations of pituitary solution stimulate normal contractions of the uterus; in these experiments, any effective dose led to the increase in tone which was equivalent to tetanus.



4. Pregnant human uterus: Removed at term Caesarian section. Fundic strip. Oxygenated Locke's solution, 37°C. At first signal immersed in pituitary solution; 1 to 1000 in Locke's solution; at second signal, plain Locke's solution. Time intervals, 1 minute.

These results harmonize quite well with those of the previously reported experiments on the uteri of cats and dogs, indicating clearly that pituitary solution is even more prone than ergot to cause a persistent contraction of the uterus. Absolutely no basis could be found for the statement that low concentrations of pituitary solution stimulate normal contractions of the uterus; in these experiments, any effective dose led to the increase in tone which was equivalent to tetanus.



5. Non-pregnant myomatous uterus—hysterectomy. Fundic strip. At first signal, immersed in Ergot suspension, 1 to 1000. Increase in tone persisting 80 seconds. At second signal, immersed in pituitary, 1 to 2000. Tetanus persisting as long as strip was in solution.

This effect of pituitary solution on the isolated human uterus serves well to

explain the unfortunate results that have followed the clinical use of the drug; the persistent increase in intra-uterine pressure acting deleteriously on the child, and also tending to produce perineal lacerations or even uterine rupture. That such results invariably follow the use of pituitary solution is disproved by the many cases where the administration of the drug does no harm; the fact remains, however, that in patients where all the indications were present and where the attendant possessed undoubted skill, the employment of pituitary solution has, too often, led to serious or even fatal results to mother, child, or both.

BIBLIOGRAPHY.

- (1) *Journal of the A. M. A.*, LXXVI, p. 1390. May 21, 1921. Rucker and Haskell: "The dangers of pituitary extract."
- (2) *Rev. Francaise de Gym. et d'Obstetrique*, XIX, p. 65. Feb. 10, 1924. Rucker and Haskell: "Uterine rupture and maternal death after employment of pituitary solution."
- (3) "A Manual of Midwifery," p. 137.
- (4) *Am. J. Obst. and Gynecology*, IV, p. 1, Dec. 1922. Haskell and Rucker: "The action of ergot and solution of hypophysis on the uterus."
- (5) *Proc. Roy. Soc.*, LXXXVII, p. 551, 1913-14. Gunn: "The action of certain drugs on the isolated human uterus."
- (6) *Am. J. Obst. and Diseases of Women and Children*, LXXI, p. 209, Feb. 1915. Lieb: "The physiology and pharmacology of the excised human uterus."
- (7) *Bull. J. H. Hosp.*, XXXVI, p. 280. April 1925. Ko Chi Sun: "Spontaneous contractions of the pregnant human uterus."

LABORATORY OF PHARMACOLOGY,
MEDICAL COLLEGE OF VA.

THE ASSAY OF MINNESOTA AND OTHER SAMPLES OF DIGITALIS.*

BY E. L. NEWCOMB AND E. B. FISCHER.

It has been customary for us to record each year the results of the assay of digitalis produced in Minnesota. These results are not reported to the Association each year, but we have attempted to present them all at one or another of the meetings. This year the results obtained in 1922, 1923, and 1924 crops are given; these include not only the assay of the official digitalis, but also of the leaves of *Digitalis lutea*, which we are growing in considerable quantities. The summary for many tests made each year are reported.

The U. S. P. official method is the biologic one, involving the use of frogs. The method in the present Pharmacopœia will be included in U. S. P. X. This official method has been used by us for a number of years, and determines the toxicity of the drug very well. Many pharmacologists believe that the official assay method probably is not a true index of the therapeutic value of digitalis; it is a test of the amount required to kill a frog. Some hold that the toxicity is directly comparable with the therapeutic value of the drug; work which others have done shows it does not always indicate the true therapeutic value of samples of digitalis.

In our work we have been endeavoring to develop a method which would more accurately measure the therapeutic value of the digitalis. Its general effect is to lower the rate of the pulse and increase the blood pressure. If we can develop a method which will accurately give us the measurement of the percentage of reduc-

* Read before joint meeting Northwestern Branch, A. Ph. A., and Minnesota Pharmaceutical Association.