A CONTRIBUTION TO THE PHARMACOLOGY OF ERIOCOMA FLORIBUNDA.

BY G. G. COLIN.*

Accidents due to the administration of pituitary solution are not uncommon. Dr. A. M. Mendenhall, in a recent communication to current medical literature (1), calls attention to this fact and points out the necessity of better methods of standardization that will enable the clinician to use preparations of uniform potency. Dr. Oliver Kamm and his associates have made a most valuable contribution (2) to the chemistry and pharmacology of extracts of posterior pituitary lobe, with the isolation of the pressor and oxytocic principles.

In this connection, the study of *Eriocoma floribunda* in which we have been interested for some time may prove to be a valuable therapeutic agent for the obstetrician. Many accidents have been recorded by the use of infusions and fluidextracts of this potent drug, even in the hands of competent physicians. The reason of such accidents was easily demonstrated when we made an investigation of the potency of fluidextracts, such as prepared by the pharmacist. Variations between 3 and 30 per cent were observed in potency. Since the Mexican Pharmacopœia does not require a biological assay, fluidextracts are prepared according to standard methods so that 1 cc. shall represent the active principle of 1 Gm. of material. The error of such a method is quite evident, especially so with some native medicinal plants. I have frequently pointed out that biological assays should be adopted when any given plant is known to possess principles of great potency.

PREPARATION OF THE SOLUTION.

This plant is much used by the poorer classes of people who resort to midwives rather than to the physician, perhaps for economical reasons. However, midwifery in the country is a rather empirical practice that leads to serious complications. The high infant mortality rate in the country (five times that of New York City according to statistics from the Health Department) is due, among other things, to obstetrical practice by untrained individuals. This situation has been remedied in part by the Free Dispensaries for maternity cases, established by the Health Authorities.

Ordinary infusions are commonly used to "help" labor. The potency of the drug may be estimated by the fact that weak infusions, the color of weak tea, often tetanize the uterine muscle, making delivery practically impossible, the introduction of forceps being a difficult matter in those conditions. The product is often born dead and the mother presents a picture of a severe intoxication.

In order to estimate the potency of the drug simple infusions were made to approximate the common method of administration. These infusions were made using 5, 10 and 20 Gm. per 100 cc. of water. The water was maintained at a temperature of about 75° C. for 10 minutes and then filtered. A fluidextract was also prepared using 70% alcohol as a menstruum and 500 Gm. of the finely powdered drug. Attempts to isolate some pure substance were partially successful. Although other investigators have pointed out the possibility of the existence of a

* Submitted by author, July 20, 1929.

water-soluble alkaloid, no evidence of its presence could be found. However, by partial precipitation with alcohol in an alkaline medium, about p_H 9.5, two active fractions could be obtained which I have called Eriocomine *A* and *B*. "The appearance of "Eriocomine *A*" is much the same as that of the total dry extract; it is dark brown and highly hygroscopic. If applied at the tip of the tongue a slight sensation of anesthesia is experienced in about 5 minutes. "Eriocomine *B*" may be obtained from the *A* fraction by solution in water. The Fraction *A* will dissolve leaving *B* in the filter. The assay of both fractions has shown that *A* is the active one. A 10% solution of this fraction has already been used both for biological assay and in the clinic.

PHARMACOLOGY.

Two other investigators have devoted their scientific attention to this drug: Dr. J. Fernández de Castro in 1925 and Dr. A. Rodríguez Román, in 1929, both in their M.D. theses, at the Faculty of Medicine of the National University. Dr. Fernández de Castro used infusions and the fluidextract, and Dr. Rodríguez Román used a so-called intract (a water extract, concentrated) and the fluidextract also. Tests with the total dry extract were carried out by the former. Both investigators obtained approximately the same results which are given below.

The subcutaneous injections of 1–3 cc. of a 10% infusion cause a burning sensation while the liquid is being introduced; the pain persists for about two hours. Later on there is pain and hyperesthesia at the site of injection; there is reddening of the skin without ischemia. Formation of pus was never observed. The experiments in male and female guinea-pigs as carried out by Dr. Fernández de Castro are interesting. However, the lack of a fixed product, that is, of a solution of known potency, make the observations less accurate than would be desirable. With the injection of from 1 to 5 cc. of the 10% infusions the animals give evidence of pain. The animal loses its appetite for a few hours, remains motionless, the genitalia appear congested and respiration seems difficult. Later on the animals show signs of excitement which subside within an hour more. Other experiments were carried out by the same author using a total dry extract in small gelatin capsules. Males and some pregnant females were used in the experiment (guinea-pigs of 300–600 Gm., from 3 to 6 months old). Doses as high as 1.80 Gm. per kilo of weight were given without abortions. The genitalia, as in the first experiments, appeared congested. The males seemed to experience sexual excitement, judging by the way they followed the females.

The next experiment was carried out with pregnant females from 8 to 12 months old. The injections were given subcutaneously using the total solid extract diluted with four parts of water. From 0.36 to 1.70 Gm. per kilo were given subcutaneously, causing abortion in all animals except one, eight animals being used in the experiment; 1.70 and 1.20 Gm. per kilo caused death in two animals. On necropsy the following was observed: Three hours after death, decomposition was evident. The hair came off easily. The vulva was swollen and half open with some blood. There was no pus at the site of injection. The stomach and intestines showed evidence of hemorrhage. The uterus was highly congested; it contained five small animals; the placenta was partially destroyed and separated from the congested uterus. The liver gave evidence of hemorrhage, it was dark

in color, especially along the edges; the kidney was hard and congested; the suprarenal capsules presented the same picture. By compression of the bladder a few drops of normal urine were obtained. The heart was highly dilated, in diastole, with coagulum. There was no muscular rigidity or congestion of the striated muscle.

The action on the isolated uterus, as reported by Fernández de Castro, is as follows: The contractions are rather irregular at first. They last from 20 seconds to 2 minutes with intervals of 20 seconds. Each uterus can be excited by the drug as long as eight hours after excision. *In vivo* it may be observed that the uterus suffers contractions. Cardiac and respiratory movements are not appreciably affected. Large doses introduced by the vein do not affect respiratory movements. The substance has no coagulating effect. Blood pressure is not affected.

PHYSIOLOGICAL ACTION OF ERIOCOMINE.

Our 10 per cent solution has been used throughout our experiments with the Fraction *A*. The results are similar to those obtained by the other investigators, differing in that the exact knowledge of the amount of substance given enabled us to exert better control in the effects observed.

We have also used infusions and fluidextracts prepared by ourselves. However, we were able to observe that intense effects on blood pressure and lack of uniformity of results were always sources of error. This lack of uniformity has frequently been reported by physicians when prescribing the fluidextract. The exact nature of Fraction *A* is still unknown, although we know that it is the physiologically active substance.

Local Action.—A few drops of solution applied to the tip of the tongue give a slight sensation of anesthesia which appears within 5 minutes and lasts for about 30 minutes. Subcutaneously, 1- and 2-cc. doses are painful. However, no induration appears as observed with infusions by Fernández de Castro, nor does the painfulness last 10 to 15 days. There is slight local hyperemia and pain for two or three days only.

Action on Isolated Uterus.—By the U. S. P. X method the following results have been recorded: Rythmic contractions are obtained; they increase in intensity and duration, the period of contraction being approximately 30 minutes. The maximum is reached in about 20 minutes. Doses larger than 0.50 Gm. tetanize the uterus.

Effect on Blood Pressure and Coagulability of the Blood.—No modification of blood pressure could be observed in the dog. The equivalent of 25 Gm. was given by the femoral vein without coagulating the blood nor affecting blood pressure. The effect of the total extract or of infusions is variable. Blood pressure may increase or decrease with different lots of drug.

Effect on Muscle.—The action is selective for unstriated muscle, and is best demonstrated in the uterus.

CLINICAL OBSERVATIONS.

This drug has been studied in the clinic in past years. In 1893, Arturo Mendez (3) reported some observations on uterine involution, recorded from 150 cases treated with 2 per cent infusions. The period of involution was always appre-

ciably shortened. Contemporary gynecologists have used it with excellent results in *post-partum* hemorrhage. However, it should never be used before the expulsion of product and placenta. Its indiscriminate use has caused serious accidents. The pathological anatomy as observed at necropsies of intoxicated women show a picture very similar to that described for animals killed with large doses of the drug. The uterus and peritoneal cavity are always found severely congested. The uterus appears enlarged and hard. The placenta appears torn and half detached. Perforations in the upper part of the vagina going into the peritoneal cavity have been observed. The heart is always found paralyzed in systole, a fact that does not agree with the observations in the animal where the heart stops in diastole.

COMMENTARIES.

Eriocoma floribunda is a very potent drug. Its empirical use, due to lack of knowledge of its active principle, has been known to cause serious accidents even in the hands of competent physicians. By furnishing this 10 per cent solution clinicians report consistently good results. We have had many requests for samples and literature from physicians and from pharmacological laboratories. In order to accommodate those interested, since the only available literature is in Spanish, this report has been prepared from the original read at a recent meeting of the Mexican Chemical Society (4). The original report being rather extensive, only the most important facts are transcribed here. The substance in question is not commercially available. Material for clinical experimentation has been furnished by this laboratory to those pharmacologists and physicians who have expressed their interest in the investigation. The original paper, in Spanish, will be published in one of our scientific journals at an early date.

CONCLUSIONS.

The following may be drawn from the data so far available from animal and human experimentation:

1. The physiological action of *Eriocoma floribunda* has been investigated.
2. Two fractions which have been called "Eriocomine *A* and *B*" have been isolated. Eriocomine appears to be the active principle of the drug.
3. Eriocomine has oxytocic effects similar to those of ergot and of pituitrin. It differs from them in that it has no appreciable effect on blood pressure.
4. The drug will stimulate uterine contractions, *in vivo* and *in vitro*, by peripheral action.
5. It acts specifically on unstriated muscle.
6. The plant contains a large amount of inert material which must be removed to avoid side actions which may introduce considerable error in the observations.
7. Eriocomine has been used successfully to combat *post-partum* hemorrhage and to stimulate uterine involution. Its use to stimulate uterine contractions during labor seems to be dangerous. Until the action of the drug is better known, it should never be used before delivery. Its specific indication seems to be in *post-partum* hemorrhage, and in other forms of hemorrhage from the uterus, non-adrenal.

8. Further clinical study is needed to estimate the uses and limitations of this new oxytocic.

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(2) O. Kamm and associates, *J. A. C. S.*, 50, No. 2573 (1928), 601.

(3) Quoted by Fernández de Castro, M.D. *Thesis*, 1925.

(4) G. G. Colin, *Consideraciones acerca de la Farmacologiá y Normalización de los ocitócicos, con especial referencia al estudio del Zoapalle.*—Unpublished report. Read at the May meeting (1929) of the Mexican Chemical Society.

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PARA-METHOXY CINNAMIC ACID. A REVISION.

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Synonymy:

1. Methyl par(a)oxy phenyl acrylic acid[1] (1878).
2. Methyl ether of paracoumaric acid[2] (1887).
3. Methylnaringeninsaeure[3] (1887).
4. Methyl paracoumaric acid[4] (1881).
5. Para methoxy phenyl acrylic acid[5] (1918).

History.—Para-methoxy cinnamic acid was first prepared by Perkin[6] in 1877. Its ethyl ester was observed by Thresh,[7] in 1884, in *Hedychium spicatum*. Van Romburg,[8] who, in 1900, found that the larger part of the oil of *Kaempferia Galanga* consisted of this crystalline ester, supposed that he had noted its first occurrence in nature.

Occurrence.—Free or as ethyl ester it has been found in the following plants:

Hedychium spicatum, Ham. (Fam. *Zingiberaceæ*). Thresh[9] discovered the ethyl ester in 1884 in the oil of the rhizome.

Kaempferia Galanga Linné (Fam. *Zingiberaceæ*) Van Romburgh,[10] in 1900, found that the larger part of the oil distilled from the rhizome consisted of this crystalline ester. This was substantiated by Panicker, Puthan, Rao & Simonsen[11] in 1926.

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[1] Perkin, *J. Chem. Soc.*, 33, p. 211.

[2] Eigel, *Ber.*, 20, p. 2527. Coumaric acids are hydroxy cinnamic acids.

[3] Will, *Ibid.*, 20, p. 294. Naringeninic acid is *p*-hydroxy cinnamic acid, originally so-called because, with phloroglucinol, it results upon hydrolysis of naringenin, which, in turn, is obtained upon hydrolysis of the glucoside hesperidin.

[4] Koerner and Menozzi, *Gaz. Chim. Ital.*, 11, p. 549.

[5] Matzuo, *J. Biol. Chem.*, 35, p. 291.

[6] *J. Chem. Soc.* (3), 1, p. 388.

[7] *Pharm. J.*, 44, p. 361.

[8] *Königl. Akad. Wet. te Amsterd.*, 3, p. 38.

[9] *Pharm. J.*, 44, p. 361.

[10] *Königl. Akad. Wet. te Amsterd.*, 3, p. 38.

[11] *J. Indian Inst. Sci.*, 9A, p. 133.