In this section, the oxytocics, uterine sedatives and hemostatics, abortifacients, and spermaticides are discussed. The drugs of endocrine origin affecting the reproductive system are treated elsewhere.

CHAPTER 36

OXYTOCICS

ERGOT, ERGOT ALKALOIDS AND POSTERIOR PITUITARY

Oxytocics are drugs which stimulate the motility of the uterus. Although much is known about the physiology of the uterus, factors controlling uterine motility are incompletely understood. The uterus contains smooth muscle which exhibits all the properties characteristic of this type of tissue. The organ contracts spontaneously and rhythmically even in its prepuberal state. When the uterus is fully developed, contractions are more marked and its activity varies with different periods of the menstrual cycle. The pregnant uterus is a very motile organ and at term the uterine contractions play an important rôle in the expulsion of the fetus. It is not known, however, what constitutes the stimulus for the initiation and perpetuation of the extreme uterine activity which characterizes labor.

The uterus receives both cholinergic and adrenergic autonomic fibers, the former from the pelvic nerve and the latter from postganglionic fibers from the inferior mesenteric and hypogastric ganglia. However, the responses of the uterus to the stimulation of these nerves and to autonomic drugs are not marked and vary in different species and in the pregnant and nonpregnant state. In human beings, the stimulation of both sympathetic and parasympathetic nerves produces increased uterine motility. The response is more prominent in the pregnant uterus. Nevertheless, complete denervation of the uterus causes little or no change in motor activity. For practical purposes, one may dismiss the action of autonomic drugs upon the uterus as unimportant.

There is, however, a group of drugs which have a pronounced effect on uterine motility. Their action is quite selective for, although other smooth muscles are stimulated, uterine excitation is much more pronounced. These drugs comprise the clinical oxytocics. The most important are three alkaloids obtained from ergot, ergotoxine, ergotamine, and ergonovine (ergometrine), and the oxytocic principle extracted from the posterior lobe of the hypophysis. In addition, histamine and quinine have a marked effect on uterine muscle. This does not, by any means, complete the list of drugs which can affect uterine motility but, with the exception of histamine, the aforementioned drugs are those which are used clinically for their oxytocic action.
Anthony's fire, the latter name being in honor of the saint at whose shrine relief was said to be obtained. The relief which followed migration to the shrine of St. Anthony was probably a real one, for the peasants who developed their symptoms as a result of ingesting contaminated grain obtained a complete change of diet during their sojourn at the shrine. The symptoms of ergot poisoning were not restricted to the limbs. Indeed, a frequent complication of ergot poisoning was abortion. A convulsive type of ergotism was also known. There still is no proved explanation as to why, in certain instances, ergotism was associated with symptoms referable to the central nervous system. It has been suggested that the convulsive form of ergotism occurred in persons with vitamin deficiency.

It was not until 1670 that ergot was proved to be the cause of the destructive epidemics which, for centuries, had raged uncontrolled. At present, our knowledge of the etiology of ergot poisoning makes its prevention quite simple. Yet, outbreaks of ergot poisoning have occurred in the present century, epidemics having been reported in Russia in 1926 and in Ireland in 1929.

A fungus growing on corn and causing “corn-smut” (Ustilago maydis) is analogous to that found on rye and has been the cause of small outbreaks of maize poisoning, especially in the northern Mediterranean countries.

Ergot was known as an obstetrical herb before it was identified as being the cause of St. Anthony's fire. It was mentioned as early as 1582 by Lonicer as a proved means of producing pains in the womb. For years it was used by midwives before it was recognized by the medical profession. The first physician to employ ergot was Desgranges, but he did not publish his observations until 1818. Before that time, a letter published by John Stearns (1807) in the Medical Repository of New York entitled, “Account of the Pulvis parturiens, a Remedy for quickening Child-birth,” marked the introduction of ergot into official medicine (Thoms, 1931). This communication is of sufficient historical interest to quote certain pertinent portions of it: “It (Pulvis parturiens) expedites lingering parturition and saves to the accoucheur a considerable portion of time, without producing any bad effects on the patient. ... Previous to its exhibition it is of the utmost consequence to ascertain the presentation ... as the violent and almost incessant action which it induces in the uterus precludes the possibility of turning ...”

“If the dose is large it will produce nausea and vomiting. In most cases you will be surprised with the suddenness of its operation; it is, therefore, necessary to be completely ready before you give the medicine. ... Since I have adopted the use of this powder I have seldom found a case that detained me more than three hours. ...”

The use of ergot in the United States spread rapidly, but its adoption in Europe was delayed, perhaps, as Barger (1931) has suggested, because the Old World had suffered too much from the poisonous properties of ergot. The dangers attending the use of the drug, however, were soon recognized. In 1824, Hosack wrote that the number of stillborn children had increased so greatly since the introduction of ergot that the medical society of New York instituted an inquiry. Said Hosack, “The ergot has been called ... pulvis ad partum; as it regards the child, it may, with almost equal truth, be denominated the pulvis ad mortem.” This astute observer recommended that the drug be used only to control postpartum hemorrhage. Thus, more than a century ago, the indications and contraindications of the oxytocic drugs were defined.

Chemistry. Ergot has been the object of intensive chemical investigation for many years. It is now believed that all the activity of crude ergot can be accounted for by the chemically identified products obtainable from it. Tanret, in 1875, was the first to isolate an ergot alkaloid now known as ergotinine. This substance, however, proved to be inactive. Barger and Carr (1906) obtained a pharmacologically active crystalline alkaloid, ergotoxine. In the same year, Kraft independently obtained the identical substance and thought it to be a hydrated form of ergotinine. It is now known that ergotinine and ergotoxine are optical isomers, the latter being levorotatory. In 1920 Stoll announced the discovery of two more alkaloids of ergot, ergotamine and ergotaminine. These two substances are also optical isomers. Ergotamine is levorotatory and pharmacologically active; ergotaminine is dextrorotatory and inactive.

With the isolation of these four alkaloids, two of them showing a high degree of activity and the typical actions of crude ergot extracts, it was assumed that the chemical riddle of crude ergot had been solved and that the actions of ergot were
due to these known alkaloids. As time passed, however, it gradually became apparent that the pharmacological properties of fluid extract of ergot were quite different from those of its pure alkaloids. The crude preparation was often more efficient, being more rapid in action and effective after oral ingestion. In contrast, the crystalline products which it yielded acted only after a latent period and were relatively impotent by the oral route. Once again the problem of the chemistry of ergot was attacked, this time with such vigor that four groups of investigators independently and almost simultaneously announced the discovery of a new ergot alkaloid. Dudley and Moir (1935), Thompson (1935), Stoll and Burckhardt (1935), and Kharasch and Lagault (1935) named the alkaloids which they had isolated ergometrine, ergostetrine, ergobasine and ergotocine, respectively. It was soon ascertained that these workers were dealing with the same substance, to which the Council on Pharmacy and Chemistry gave the name Ergonovine (1937). Ergonovine is levorotatory, and its dextroisomer, ergometrinine, has also been isolated.

In 1936, Smith and Timmis isolated another pair of ergot alkaloids, ergosine (levorotatory) and ergosinine (dextrorotatory). In 1937, Stoll and Burckhardt added ergocristine (levorotatory) and ergocristinine (dextrorotatory) to the growing number of pairs of ergot alkaloids.

The chemical structure of the alkaloids of ergot has been elucidated largely by the work of Jacobs and his collaborators (see review of Nelson and Calverly, 1938). All are derivatives of lysergic acid, an indole derivative. The optical isomerism of the alkaloids of ergot is due to the presence of an asymmetric carbon atom in the lysergic acid portion of the molecule. Only the levorotatory member of each pair possesses marked pharmacological activity. Ergonovine upon hydrolysis yields lysergic acid and hydroxy isopropylamine. The alkaloids of higher molecular weight hydrolyze to ammonia, a keto-acid and two amino acids in addition to lysergic acid. The empirical formulas of several pairs of ergot alkaloids are given in Table 34. The probable structural formulas of lysergic acid, ergonovine and ergotoxine are as follows:

### Table 34

<table>
<thead>
<tr>
<th>Alkaloid</th>
<th>Empirical Formula</th>
<th>Optical Rotation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ergotoxine</td>
<td>C_{19}H_{23}O_{2}N_{5}</td>
<td>Levo</td>
</tr>
<tr>
<td>Ergotinine</td>
<td>C_{19}H_{23}O_{2}N_{5}</td>
<td>Dextro</td>
</tr>
<tr>
<td>Ergotamine</td>
<td>C_{19}H_{23}O_{2}N_{5}</td>
<td>Levo</td>
</tr>
<tr>
<td>Ergotaminine</td>
<td>C_{19}H_{23}O_{2}N_{5}</td>
<td>Dextro</td>
</tr>
<tr>
<td>Ergonovine</td>
<td>C_{19}H_{23}O_{2}N_{5}</td>
<td>Levo</td>
</tr>
<tr>
<td>Ergometrine</td>
<td>C_{19}H_{23}O_{2}N_{5}</td>
<td>Dextro</td>
</tr>
<tr>
<td>Ergostetrine</td>
<td>C_{19}H_{23}O_{2}N_{5}</td>
<td>Levo</td>
</tr>
<tr>
<td>Ergobasine</td>
<td>C_{19}H_{23}O_{2}N_{5}</td>
<td>Dextro</td>
</tr>
<tr>
<td>Ergotocine</td>
<td>C_{19}H_{23}O_{2}N_{5}</td>
<td>Levo</td>
</tr>
<tr>
<td>Ergostetrinine</td>
<td>C_{19}H_{23}O_{2}N_{5}</td>
<td>Dextro</td>
</tr>
<tr>
<td>Ergometrinine</td>
<td>C_{19}H_{23}O_{2}N_{5}</td>
<td>Levo</td>
</tr>
<tr>
<td>Ergosine</td>
<td>C_{19}H_{23}O_{2}N_{5}</td>
<td>Dextro</td>
</tr>
<tr>
<td>Ergosinine</td>
<td>C_{19}H_{23}O_{2}N_{5}</td>
<td>Levo</td>
</tr>
<tr>
<td>Ergocristine</td>
<td>C_{19}H_{23}O_{2}N_{5}</td>
<td>Dextro</td>
</tr>
<tr>
<td>Ergocristinine</td>
<td>C_{19}H_{23}O_{2}N_{5}</td>
<td>Dextro</td>
</tr>
</tbody>
</table>

* Pharmacologically active compounds used in therapeutics.
Pharmacological Actions of Ergotoxine and Ergotamine. The pharmacological actions of ergotoxine and ergotamine are so nearly identical that they will be discussed together. Ergonovine, on the other hand, is quite distinct in several important respects and will therefore be given separate consideration.

**Uterus.** The most important action of ergotoxine and ergotamine is on the uterus. The effects of the two alkaloids on this organ are identical. The motor activity of the uterus is markedly increased. The type of contraction exhibited is related to the dose of drug administered. After small amounts, uterine contractions are quite normal in character and are followed by relaxation. After large doses, the contractions are more powerful and spastic in nature. The sensitivity of the uterus to ergot alkaloids varies, especially with the degree of maturity and the stage of gestation. Even an immature uterus is stimulated by the drugs. The gravid uterus, however, is much more sensitive and when small doses of ergot alkaloids are given at term or immediately postpartum it is possible to obtain a marked uterine response unaccompanied by any side-actions. There is little doubt that the mechanism of action is a direct muscular stimulation, and the isolated uterus responds equally as well as the uterus in situ.

**Other Smooth Muscle.** The action of ergotoxine and ergotamine on the uterus is quite selective because all smooth muscles are not similarly affected. For
example, the action on gastro-intestinal motility is negligible. In some animals, notably the cat, ergot alkaloids cause marked miosis due to a direct action on the sphincter muscle of the iris.

Circulatory System. Following the administration of large doses of ergotoxine or ergotamine, there is an increase in blood pressure which results from constriction of the smaller blood vessels. The site of this action is peripheral for vasoconstriction occurs after section of the vasomotor nerves. In all probability, the action is a direct muscular one. Ergotoxine and ergotamine also have some effect on the heart, therapeutic doses usually causing a noticeable bradycardia. This may be a reflex response to the vasoconstriction. On the other hand, these alkaloids possess, to a significant degree, the property of inactivating cholinesterase and their action in slowing the heart may, in part, be similar to that of physostigmine.

Ergotamine and ergotoxine damage the capillary endothelium. The mechanism of this toxic action is not understood. Vascular stasis, thrombosis and gangrene result and cause the prominent features of ergot poisoning. When the alkaloids are injected into roosters, the comb and wattles become cyanotic and cold, and eventually gangrenous. This vascular phenomenon provides the basis for the U.S.P. bio-assay of ergot. The susceptibility of different species to gangrene produced by ergot varies greatly. Man is peculiarly sensitive.

Sympathetic Nervous System. Ergotoxine and ergotamine paralyze the excitatory responses to epinephrine and adrenergic nerve impulses. This phenomenon is fully discussed elsewhere (pages 340, 482).

Central Nervous System. The action of ergotoxine and ergotamine on the central nervous system is variable and, as a rule, unimportant. Small doses may mildly stimulate the respiratory center. In the laboratory, the intravenous injection of large amounts of the alkaloids in anesthetized animals is likely to cause respiratory arrest due to medullary depression. After toxic doses in man, vomiting is a frequent symptom. The cause is not understood. Large doses of ergotoxine and ergotamine given intravenously in certain laboratory animals produce marked excitement, sham rage and other evidence of stimulation of central sympathetic centers.

Absorption, Fate and Excretion. Little is known of the fate and excretion of the ergot alkaloids. Information on the rate of absorption, however, has accumulated from clinical observations. Ergotoxine and ergotamine are poorly and irregularly absorbed from the gastro-intestinal tract. The effective oral dose is three to four times the intramuscular dose, and even then the resulting action is unpredictable (Figure 74). There is a latent period of approximately twenty minutes between the intramuscular injection of the drugs and the onset of uterine response. The action is quite long in duration, however, and may persist for several hours.

Ergonovine (Ergometrine). Ergonovine shares with ergotamine and ergotoxine the property of causing uterine stimulation, and the character of the uterine contractions which it produces does not differ from that described previously. Ergonovine, however, is much more rapid in action for the uterine response occurs almost immediately after intravenous injection of the drug and within a few minutes after intramuscular or oral administration. Ergonovine thus differs from ergotoxine and ergotamine in that it is readily absorbed from the gastro-intestinal tract. The sensitivity of the uterus to ergonovine is very great, and in pregnant women an intravenous dose of as little as 0.1 mgm or an oral dose of only 0.25
mgm results in a marked response. The action of the drug persists for several hours (Figure 74).

The effects of ergonovine on sympathetically innervated structures are in sharp contrast to those of ergotoxine and ergotamine. Ergonovine is not sympatholytic, and it appears to stimulate certain effector organs in a manner similar to sympathomimetic drugs. For example, it causes mydriasis after instillation into a rabbit’s eye, vasoconstriction when perfused through a frog’s limb, and relaxation of the isolated rabbit intestine. On the other hand, unlike a true sympathomimetic drug, ergonovine causes little or no rise in blood pressure when injected intravenously in anesthetized cats and dogs.

Ergonovine shares with ergotoxine and ergotamine the ability to produce gangrene. In the case of ergonovine, however, this property has been demonstrated only in experimental animals. There have been no clinical reports of the occurrence of gangrene in human beings following the use of ergonovine. The acute toxicity of ergonovine in animals is only about one-quarter that of ergotoxine and ergotamine. The pharmacology of ergonovine has been investigated, especially by Brown and Dale (1935), and has been reviewed by Smith (1938).

Fluidextract of Ergot. The clinical importance of fluidextract of ergot has diminished since the discovery of ergonovine. Prior to 1935, the fluidextract was often employed because it was the only type of ergot preparation which was active by mouth, and also because it had a more rapid onset of action than the pure alkaloids available up to that time. It had the disadvantage of being unstable and

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**Figure 74.** The effect of ergonovine on the human uterus.

*A.* The effect on the human uterus of 3 mgm of orally administered ergotamine or ergotoxine as compared with 0.2 mgm of ergonovine. The record is that of the uterine motility of a woman (para 4) seven days post partum, obtained by means of a balloon and manometer. Note the inefficacy of ergotoxine and ergotamine when given by mouth and the prompt and sustained response to the small dose of ergonovine. *B.* The effect of 0.2 mgm of ergonovine, given intravenously, on the uterine motility of a woman (para 2) seven days post partum. Note the immediate, marked and sustained response. (After Davis, Adair and Pearl, 1936. Courtesy of The Journal of the American Medical Association.)
very liable to deterioration. It is now appreciated that the desirable properties of the fluidextract are due mainly to the presence of ergonovine. Ergonovine, now being clinically available, promises largely to replace the fluidextract of ergot in obstetrical therapy.

**Bio-assay.** Fluidextract of ergot varies in its alkaloidal content, depending on the activity of the dried ergot used in its preparation. It therefore must be assayed in order to standardize its potency. As has already been stated, the action on the cock's comb forms the basis of the U.S.P. assay. The fluidextract is standardized against crystalline ergotoxine ethanesulfonate so that one cc of the former is equivalent to 0.5 mgm of the latter. In Great Britain, *Liquid Extract of Ergot (B.P.)* is chemically standardized to contain 0.06 per cent of the total alkaloids of ergot.

**Ergot Poisoning.** The ergot alkaloids are highly toxic and may cause acute or chronic poisoning. Acute poisoning is rare and usually results from the ingestion of large amounts of ergot preparations in attempts at abortion. The symptoms consist of vomiting, diarrhea, unquenchable thirst, tingling, itching and coldness of the skin, a rapid and weak pulse, confusion and unconsciousness.

Chronic poisoning is more common. At present the epidemic form of ergot poisoning arising from the ingestion of contaminated grain is seldom seen. However, the alkaloids of ergot are extensively employed in therapeutics, and poisoning from their injudicious administration is not rare. Poisoning is usually due to overdosage. There are indications, however, that increased sensitivity to ergot alkaloids may accompany febrile and septic states and diseases of the liver. Thus many cases of ergot poisoning have been reported in patients with puerperal fever. Also several fatalities from gangrene have occurred in patients with liver damage who received ergotamine for relief of the accompanying pruritus. Apparently in such cases there is unusual vascular sensitivity to ergotamine, because the drug has been extensively employed in the treatment of migraine without serious toxic manifestations. The presence of peripheral vascular disease also constitutes a contraindication to the use of the ergot alkaloids. Fatal poisoning has occurred after the oral administration of 26 mgm of ergotamine over a period of several days, and also following single injections of only 0.5 to 1.5 mgm.

Circulatory symptoms are the first to become evident. Gangrene starts in the extremities, usually in the toes but also in the fingers. Two factors are involved in the impairment of the circulation. Vasoconstriction is one of these but this alone is not sufficient to cause the marked vascular stasis which is observed. Lesions of the intima also develop and result in thrombi which may completely occlude the smaller arteries. A detailed description of the pathological changes observed in blood vessels following clinical ergot poisoning has been given by Yater and Cahill (1936). Circulatory disturbances other than those associated with vascular injury have been reported. Anginal pain, tachycardia or bradycardia, and elevation or lowering of the blood pressure may occur.

In addition to circulatory disturbances, other symptoms of ergot poisoning appear. The most common of these are headache, nausea, vomiting, diarrhea and dizziness. Also there may be noticed weakness, paresthesia, itching, and coldness of the skin. Symptoms referable to the central nervous system are confusion, depression, drowsiness, convulsions, hemiplegia, and tabetic manifestations. In some patients, a fixed miosis may be seen.

**Treatment.** The treatment of ergotism consists in complete withdrawal of the offending drug and symptomatic measures. The latter especially include attempts to maintain an adequate circulation to the affected parts. Vasodilators such
as the choline esters, nitrates and especially papaverine may be tried. If gangrene
impends, passive vascular exercise or intermittent venous occlusion may be re-
sorted to in addition to the usual mechanical and surgical procedures. Nausea and
vomiting may be relieved by atropine. Therapy of the milder toxic symptoms
seen after ergotamine is discussed on page 486.

Preparations. Ergot, U.S.P., B.P., is the dried sclerotium of Claviceps pur-
purea. It is not prescribed as such. Fluidextract of Ergot, U.S.P. (Liquid Extract
of Ergot, B.P.), has been described above. It is the preparation of choice among
the galenicals. Prepared Ergot, B.P., and Extract of Ergot, N.F., are inferior to the
fluidextract. Ergot Aseptic, N.N.R., is a liquid extract of ergot prepared for
parenteral administration and marketed in ampules containing one cc of sterile
solution. The potency of the product is adjusted to be the same as the official
fluidextract.

The purified alkaloids of ergot are also available for therapeutic use. Ergota-
mime tartrate consists of colorless crystals soluble in water to the extent of 1:500.
It is marketed as Gynergen, N.N.R., and is available in 0.5 and 1.0 cc ampules,
containing 0.25 and 0.5 mgm of the drug, respectively, as a 0.1 per cent solution
and in tablets containing 1.0 mgm each. Ergotoxine Ethanesulphonate, B.P., is
seldom used in the United States. It is included in the U.S.P. only as a reference
standard. It consists of a colorless, crystalline compound, sparingly soluble in
water. Ergonovine (Ergometrine, B.P.) is a colorless, crystalline substance slightly
soluble in water. It is not an official drug in the United States but is available
under the name Ergotrate. Ergotrate-H is the hydracrylate of ergonovine and is
marketed in ampules containing 0.2 mgm of the salt in sterile aqueous solution
for intravenous or intramuscular injection. Ergotrate is the malate salt and is
marketed in tablets containing 0.2 mgm for oral or sublingual administration.

Therapeutic Uses. The actions of the ergot alkaloids on the uterus and blood
vessels provide the basis for their chief therapeutic applications. The clinical use
of ergot in obstetrics is discussed in conjunction with the other oxytocics (page
667). The use of ergotamine in migraine and certain other disorders is described
under the autonomic drugs (page 483).

POSTERIOR PITUITARY

The posterior pituitary is a source of at least two substances possessing
marked pharmacological activity. Also, extracts of this gland, when given paren-
terally, have three distinct actions. They stimulate the uterus (oxytocic action),
cause peripheral vasoconstriction (pressor action) and act upon the renal tubules
to enhance water reabsorption (antidiuretic action). The extraction of such ac-
tive substances from a gland of internal secretion has led to the assumption that
the extractives are hormones. The hormonal nature of the antidiuretic principle
of the posterior pituitary is more firmly established than that of the other active
constituents of the posterior lobe (page 647).

The pharmacology of posterior pituitary extract will be described here be-
cause many available preparations possess the three aforementioned actions. The
fact that the posterior pituitary is discussed under the oxytocic drugs does not
minimize the importance of its vasoconstrictor and antidiuretic principles.

Nature and Chemistry. The question whether the pharmacological activity of
the posterior pituitary is due to the presence of a single substance or to several
substances is still being debated. Kamm and coworkers (1928) separated two active fractions from posterior pituitary extract. One possesses marked oxytocic activity and the other is strongly vasopressor and antidiuretic. The separation is not absolute, however, for each of the two fractions is contaminated by the other to the degree of approximately one per cent. Kamm and his associates, therefore, believe that there are two separate chemical entities responsible for the activity of posterior pituitary extracts. On the other hand, Abel (1930) was of the opinion that a single chemical substance is responsible for all the pharmacological activity and that the apparent separation achieved by Kamm resulted from the breakdown of an original single molecule into two active components. (Also see Rosenfeld, 1940.) The vasopressor-antidiuretic principle of the posterior pituitary has been further fragmented by Heller (1939). Heller has shown that the antidiuretic factor is more stable than the pressor factor over a wide pH range, and he has succeeded in preparing solutions of posterior pituitary which retain potent antidiuretic activity but which have lost most of their pressor effect. Heller believes the two actions reside in chemically different principles.

The practical points to be kept in mind are the following. Simple extracts of posterior pituitary always exhibit the three types of activity. There are commercially available products in which either the oxytocic activity or the vasopressor-antidiuretic activity predominates almost to the exclusion of the other. No separation has been made, in commercial preparations, of the vasopressor and antidiuretic principles.

Comparatively little is known of the chemical composition of the active constituents of posterior pituitary. Stehle and Fraser (1935) are of the opinion that they are polypeptides with a minimal molecular weight of approximately 2000, and Stehle and Trister (1939) identified several amino acids in the products of hydrolysis of purified preparations. The activity of pituitary extracts is readily destroyed by hydrolysis with dilute acid or alkali. There is likewise evidence that potency is lost after subjecting pituitary extracts to reducing agents. The enzymes of the gastro-intestinal tract also destroy posterior pituitary principles which are therefore totally ineffective when administered orally.

**Pharmacological Actions.** *Uterus.* Pituitary extract causes marked stimulation of the uterus. The action is a direct one on the myometrium, and is highly selective. The principle in pituitary extract responsible for uterine stimulation can be separated from the component which causes constriction of the smooth muscle of blood vessels, and has been called the *oxytocic principle* of the posterior pituitary. Several factors modify the response of the uterus to pituitary extract. Whereas small doses merely augment the tone and increase the amplitude of the contractions, further administration of the drug results in uterine tetany lasting five to 10 minutes (Figure 75). The uterus is more sensitive to pituitary extract during the first two weeks of the menstrual cycle. Furthermore, the uterus becomes more reactive as pregnancy progresses (Robson, 1933; Moir, 1934). These alterations in sensitivity are believed to result from the action on the uterus of the ovarian and luteal hormones. Estrone intensifies and progesterone diminishes the response of the uterus to pituitary extract (Bell and Robson, 1958). The two hormones cause a similar variation in the responsiveness of the uterus to the ergot alkaloids.

All portions of the uterus are not equally stimulated by pituitary extract. Newton (1937) showed in experimental animals that the cervix of the uterus does not respond even to high concentrations of the drug. He believes that the coordinated type of uterine contraction involving only the fundus in response to pituitary extract would be efficacious at parturition.