The actions and functions of oxytocin in relation to the pregnant human uterus will be given special attention. Other aspects will be briefly reviewed with emphasis on recent work. The pharmacology of oxytocin and of related octapeptides has been reviewed by Van Dyke (1960) and by Berde & Cerletti (1960).

EFFECTS OF EXOGENOUS OXYTOCIN

(1) Renal effects. In dogs and rats oxytocin modifies renal pressor function (RPF) and urinary excretion of water, sodium, potassium and chloride. The effects vary with the dose, the rate of urine flow and the species. The kidney of man, however, seems to be refractory to oxytocin (Pickford 1960).

(2) Cardiovascular effects. In men and non-pregnant women the rapid intravenous injection of oxytocin (200 to 600 mU) causes dilatation of skin and muscle vessels, a drop in blood pressure and a rise in cardiac output (Pickford 1960). Similar effects are produced by the macroinfusion (1000 to 8000 mU/min) of oxytocin intravenously. The effects are transient and disappear after 30 minutes despite continuation of the macroinfusion. In pregnant women the initial fall in arterial blood pressure is followed by a rise which lasts for as long as the macroinfusion is maintained (Bieniarz & Caldeyro-Barcia 1960). In diestrous or castrated rats the intravenous injection of 50 mU has no effect on blood pressure although it produces dilatation of the mesenteric vessels. In rats, at oestrus or treated with ovarian hormones or more than 10 days pregnant, oxytocin has vasoconstrictor and pressor effects (Pickford 1960).

(3) Effects on the mammary gland. Recently intramammary pressure has been recorded in puerperal women, by cannulating several mammary ducts with thin polyethylene catheters connected to pressure transducers (Sica-Blanco et al. 1959, 1960). The intravenous infusion of 4 mU/min of oxytocin (Syntocinon
Sandoz) produced rhythmical contractions of the mammary gland which were similar to those recorded during spontaneous labour and during suckling (see paragraph 17). Ten days after delivery, the rapid intravenous injection of one ml of a solution containing one mU of oxytocin per ml was sufficient to cause a rise of approximately 20 mm Hg in the milk pressure. Thus the woman appears to be more sensitive to oxytocin, per kg of body weight, than the post-partum rabbit, in which one mU is also the threshold dose for the milk ejection effect when the intravenous route is employed. By injecting oxytocin into the arterial supply of the mammary gland of the rabbit, the threshold dose can be greatly reduced (Fitzpatrick 1960; Gonzalez-Panizza et al. 1960).

Méndez-Bauer et al. (1960) have recently recorded isometric contractions produced by oxytocin in isolated strips of mammary gland obtained from the post-partum rabbit and other rodents. Responses were obtained with concentrations as low as 0.1 mU/ml. Within wide limits (0.1 to 10 mU/ml) the relationship between concentration and response was reasonably linear and remained very stable for several hours. Owing to these properties and to the absence of spontaneous contractions, this preparation offers considerable advantages over other tests currently employed for the assay of oxytocin.

(4) Uterine effect. The action oxytocin on the pregnant and non-pregnant uterus of cows and rabbits have been studied “in vivo” by Fitzpatrick (1957) and by Cross (1958 a, b) respectively. The effects of the hormone in different parts of the pregnant and nonpregnant human uterus have been studied “in vitro” by Sandberg et al. (1960).

(5) Pregnant human uterus. During the last 8 weeks of pregnancy pure synthetic oxytocin given by continuous intravenous infusion at “physiological” rates (1 to 8 mU/min) causes a marked increase in the intensity and frequency of uterine contractions without significantly raising uterine tonus. Oxytocin accelerates and coordinates the spread of the contractile wave through the uterus (Caldeyro-Barcia et al. 1957, 1959). Tracings of amniotic fluid pressure, intramyometrial pressure and the electrohysterogram (Larks et al. 1959) detect no differences between the contractions produced by oxytocin and those of normal, spontaneous labour. Furthermore, both types of contractions have equivalent efficiency in effacing and dilating the uterine cervix and in accomplishing delivery (Alvarez & Cibils 1960).

(6) Development and disappearance of uterine response. After the onset of an infusion the intensity and frequency of uterine contractions rise progressively, and take from 15 to 60 minutes before becoming stabilized. Uterine tonus is not affected by infusion rates up to 4 mU/min. Rates from 4 to 16 mU/min produce a transient rise of tonus lasting less than 15 minutes.

After cessation of the infusion, the frequency of the contractions diminishes before the intensity. If descending uterine activity is plotted against time an exponential curve is obtained. During the last 4 weeks of pregnancy the
average T50% of such curves is 15 minutes. At earlier stages of pregnancy T50% values range from 3 to 13 minutes (Sica-Blanco & Sala 1960).

(7) **Dose-response relationship.** By increasing the infusion rate of oxytocin it is possible to produce at will, all the types of uterine contractility which occur spontaneously in normal labour. Uterine activity (i.e. the product of the intensity of the contractions multiplied by their frequency) increases as an exponential function of the rate of oxytocin infusion (Caldeyro-Barcia et al. 1957). In women in late pregnancy but not in labour, infusion rates of 8 to 16 mU/min are usually adequate to raise uterine contractility to maximum values recorded during normal labour: (intensity of the contractions 50 mm Hg; frequency 5 contractions per 10 min; tonus 12 mm Hg).

(8) **Overdosage of oxytocin.** Infusion rates higher than 16 mU/min cause abnormally frequent contractions (more than 5 per 10 minutes – tachysystolia), and abnormally high tonus (more than 12 mm Hg – hypertonicity). The intensity of the contractions diminishes as tachysystolia and hypertonicity develop. Very high infusion rates (8000 mU/min) cause an immediate and very pronounced rise in tonus, which may reach 50 to 80 mm Hg, devoid of rhythmic contractions. This “contracture” persists for the duration of the macroinfusion. Post-infusion recovery takes more than one hour (Poseiro & Noriega-Guerra 1960).

(9) **Mechanism of action of oxytocin on the uterus.** According to Jung (1960) and to Csapo (1960) oxytocin acts on the membrane of the myometrial cell and not on the contractile myoplasm. Oxytocin increases membrane permeability to potassium, lowering the membrane potential and thus the excitability threshold (Jung 1960). In the rat uterus, Fielitz & Gonzalez-Panizza (personal comm.), found “in vitro” that “physiological” concentrations of oxytocin (0.001 mU/ml) markedly lowered the uterine threshold to electrical stimulation, confirming Csapo’s results (1954) obtained in the rabbit uterus with higher concentrations (0.1 mU/ml) of oxytocin. These observations suggest that under the influence of oxytocin a greater number of fibers respond to each spontaneous stimulus originating in any “pacemaker” of the intact uterus. Thiersch et al. (1959) and Csapo (1960) find that oxytocin increases the duration and frequency of the spike discharge corresponding to each uterine contraction. All the above described mechanisms may explain the augmentation of the intensity of the contractions which is produced by “physiological” doses of oxytocin.

“Overdosage” of the hormone depresses the membrane potential beyond physiological limits, suppresses spike discharges, and rhythmic contractions (which are the consequence of spike discharges) cease. The uterine “tonus” depends on a contractile mechanism different from that of the rhythmic contractions and rises in linear relationship to the lowering of the membrane potential caused by overdosage of oxytocin (Jung 1960).
(10) **Comparison of the uterine effects of oxytocin and vasopressin.** In early pregnancy arginine vasopressin (ADH) and oxytocin are equiactive on the human uterus (*Embrey* 1959). As pregnancy advances the response to oxytocin is greatly augmented (see paragraph 11–1) whereas no significant change occurs in the response to ADH. In late pregnancy the effects on uterine contractions of the infusion of 64 mU ADH per minute are quantitatively equivalent to those of 2 mU oxytocin per minute. The contractions elicited by ADH are incoordinated and have an irregular rhythm whereas those produced by oxytocin are regular and well coordinated [See (5)]. The uterine tonus is increased by 64 mU/min of ADH whereas it is not affected by 2 mU/min of oxytocin (*Cibils et al.* 1960).

(11)–1 **Influence of the gestational age.** As early as the 12th week of pregnancy the human uterus gives a much greater response to oxytocin than when non-pregnant. The response markedly increases as pregnancy advances and reaches maximum values between the 32nd and the 36th week showing no significant changes during the last 1 to 2 months of gestation or during labour (See Table 1). The divergent results obtained by other workers (*Smyth* 1958; *Theobald* 1960; *Muller* 1960; *Aburel et al.* 1957) may be explained by differences in the methods employed (*Caldeyro-Barcia & Sereno* 1960).

<table>
<thead>
<tr>
<th>Weeks of pregnancy</th>
<th>12th</th>
<th>20th</th>
<th>30th</th>
<th>36th</th>
<th>40th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxytocin infusion rate (mU/min) required for producing an increment of 40 Montevideo Units in uterine activity</td>
<td>16</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Oxytocin infusion rate (mU/min) required for producing an increment of 100 Montevideo Units in uterine activity</td>
<td>100</td>
<td>16</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Average spontaneous uterine activity “Montevideo Units”</td>
<td>4</td>
<td>6</td>
<td>10</td>
<td>20</td>
<td>50</td>
</tr>
</tbody>
</table>

Infusion rates of oxytocin required at different gestational ages in order to produce increments of uterine activity of respectively 40 and 100 Montevideo Units over the spontaneous activity. The intensity of the contractions (measured in mm Hg) multiplied by their frequency (contractions per 10 minutes) is equal to the “uterine activity” in mm Hg per 10 minutes, or Montevideo Units.

(11)–2 **Species differences.** In the human, cat, cow and guineapig the uterus responds to oxytocin during most of pregnancy, reactivity increasing with gestational age and at least in the human and guineapig, maximum reactivity is reached before term. In the rabbit there is a marked difference since from the 2nd to the 29th day, the uterus does not respond at all to oxytocin (even
with very large doses) and responsiveness returns only in the last 2 or 3 days of pregnancy (Robson 1933; Schofield 1957; Csapo 1960).

(12) Progesterone and uterine response to oxytocin. In the rabbit, progesterone reduces or abolishes the contractility of the uterus and its response to oxytocin, and prevents both spontaneous and oxytocin-induced labour. According to Pose & Fiilitz (1960) the intramuscular administration of 400 mg of progesterone daily, for 4 days, to pregnant women neither produces significant reduction of the uterine response to oxytocin infusion, nor prevents spontaneous or oxytocin induced labour.

According to Short (1959), in women the blood concentration of endogenous progesterone is greatly increased over pre-existing values during the last 5 weeks of pregnancy and labour. This is the time when the uterus is most responsive to oxytocin [See (11 – 1)]. After delivery blood progesterone concentration falls very rapidly.

BLOOD CONCENTRATION OF OXYTOCIN

(13) During macroinfusions of oxytocin to pregnant women. The milk ejecting effect in the lactating rabbit was used for the assay of oxytocin. One ml of blood was injected intravenously into the rabbit approximately 15 seconds after withdrawal from a pregnant woman, in order to minimize the destruction of oxytocin by oxytocinase (see paragraph 22). In order to produce concentrations of oxytocin in the blood, detectable by this method, it is necessary to use very high rates of infusion of oxytocin (8000 to 16000 mU/min) which are designated as “macroinfusions” and which produce abnormal “contracture” of the pregnant human uterus (see paragraph 8) and for this reason can only be given to patients with a dead foetus.

The concentration of oxytocin in the blood increased during the first 20 minutes of the macroinfusion and then remained stable at a level of 13 mU/ml when the rate of infusion was 16000 mU/min. After cessation of the macroinfusion the blood concentration of oxytocin fell rapidly and the corresponding half life ranged from 1.2 to 4 minutes (Gonzalez-Panizza et al. 1960). These figures are of a similar order as the half lives of oxytocin found in rabbits by Chaudhury & Walker (1957) and in rats by Heller (1959) and by Ginsburg & Smith (1959).

(14) During “physiological” infusions of oxytocin. The milk ejection method described above was not sensitive enough to detect oxytocin in the blood of pregnant women during infusions of 8 mU/min, which elicit uterine contractions similar to those of normal labour (see paragraph 5). From the sensitivity of the assay method it was concluded that during such infusions the blood contained less than 0.5 mU of oxytocin per ml.

(15) Endogenous oxytocin. The oxytocic activity (10 mU/ml) reported by
Hawker (1960) in blood of pregnant women, is very high to be due to endogenous oxytocin, since it is similar to the values found in the author’s laboratory during macroinfusions of oxytocin (see paragraph 13) which produced abnormal uterine “contracture” (see paragraph 8). It should be recalled that several substances different from oxytocin but active on the rat uterus appear “in vitro” in the blood, plasma and serum (Croxatto et al. 1960; Vanden Driesche 1960; Hawker 1960); we consider that these substances, which do not exist in the circulating blood, may be responsible for the high values reported by Hawker.

Very recently, in the author’s laboratory working in collaboration with Dr. R. J. Fitzpatrick, an “oxytocin-like substance” (O.L.S.) has been found in the plasma obtained from parturient women. The blood was collected and centrifuged at 0° C and the cold plasma was assayed by injection into the arterial supply of the mammary gland of the lactating rabbit. This method can detect concentrations as low as 0.02 mU of oxytocin per ml. In normal labour the concentration of O.L.S. corresponded to 0.1 to 0.2 mU of oxytocin per ml of plasma and fell to 0.02 mU per ml 24 hours after delivery. When the blood (or plasma) of parturient women was not cooled immediately after withdrawal to 0° C, the O.L.S. disappeared very rapidly. At 38° C the half life of O.L.S. is of a similar order to that of exogenous oxytocin added to the plasma of parturient women (see paragraph 22).

FUNCTIONS OF OXYTOCIN

(16) It is still a matter of controversy as to whether oxytocin has any physiological role in renal or cardiovascular functions or in the transport of sperm in the female genital tract after mating. Much circumstantial evidence supports the view that oxytocin is a humoral mediator which stimulates the secretion of prolactin in the adenohypophysis. It is the role of oxytocin in the milk ejection reflex that is most widely accepted as being of physiological significance (Cross 1960).

(17) The following facts are in agreement with the opinion that oxytocin has a role in parturition:

a) In pregnant women near term but not in labour, oxytocin is the only known substance which is able to stimulate uterine contractions indistinguishable from those of spontaneous normal labour (see paragraph 5). The contractions produced by ergonovine (Embrey 1959; Smyth 1960) ergotamine, spartein and ADH are very different (see paragraph 10). Oxytocin is also able to elicit contractions of the human mammary gland which are identical to those recorded during suckling (Sica-Blanco et al. 1960).

b) The rates of oxytocin infusion (1 to 8 mU/min) which in pregnant women produce physiological stimulation of the mammary gland and of the
uterus are very small, in the order of $10^{-9}$ grams/minute/70 kg. These rates are similar to those of ADH required for inhibiting water diuresis (Theobald et al. 1948).

c) The recording of milk ejection indicates that oxytocin is released during spontaneous labour in rabbits and that equivalent amounts of exogenous oxytocin can effect delivery of living young when all supporting mechanisms are blocked by spinal and general anaesthesia (Cross 1960).

d) In some women the recording of the intramammary pressure showed marked milk ejection activity during normal spontaneous labour. The magnitude of mammary activity changed in a parallel manner with that of the parturient uterus. The activity of both organs increased as labour progressed, reached maximum values during the second stage of labour and decreased after delivery (Sica-Blanco et al. 1960).

c) In rabbits, electrical stimulation of the neurohypophysis or its nerve supply results in secretion of oxytocin (Ferguson 1941; Harris 1955; Cross 1960) and thereby greatly increased milk ejection and uterine activity which may produce parturition.

f) Significant increase of uterine contractility is produced in pregnant women by agents known to stimulate the neurohypophysis, such as intravenous injections of hypertonic NaCl (Hendricks et al 1959), morphine (Caldeyro-Barcia et al. 1955), distension of the uterine cervix and stimulation of the teats. Suckling stimulates rhythmic contractions of the uterus and of the mammary gland which are similar to the contractions recorded during spontaneous normal labour and during the infusion of oxytocin at the rate of 4–8 mU/min (Sica-Blanco et al. 1960).

g) In ewes Fitzpatrick (1960) reported significant rises in the blood concentration of endogenous oxytocin during labour and delivery and also at the commencement of suckling. The identification of oxytocin was made by pharmacological tests, paper chromatography and by inactivation with thyo-glycollate. A similar rise of an “oxytocin-like substance” has been found in the plasma of parturient women in the author's laboratory (see paragraph 15).

(18) As the response to oxytocin of the pregnant human uterus does not change either during the last weeks of pregnancy or during labour [See (11)], it is necessary to postulate an augmentation in the rate of secretion of the hormone in order to explain the great increase of uterine activity which occurs at the end of pregnancy and during labour. The maximum values of uterine activity recorded in normal labour require a secretion rate of 8 mU/min [See (6)].

(19) The neural control of oxytocin secretion has been recently reviewed by Cross (1960) who concludes: “In the mammal reflexes governing the release of oxytocin come into play in certain phases of reproduction” (coitus, labour, suckling). Our knowledge on the neural pathways involved in the
control of oxytocin secretion has been developed by Harris (1955) and by Cross (1960).

(20) It is still a matter of controversy as to whether the neurohypophysis can release oxytocin independently from ADH or vice versa.

(21) The occurrence, storage and metabolism of oxytocin have been recently reviewed by Heller (1960).

<table>
<thead>
<tr>
<th>Weeks of amenorrhoea</th>
<th>10 %</th>
<th>20 %</th>
<th>25 %</th>
<th>30 %</th>
<th>35 %</th>
<th>37-40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxytocinase activity</td>
<td>10 %</td>
<td>15 %</td>
<td>20 %</td>
<td>55 %</td>
<td>80 %</td>
<td>100 %</td>
</tr>
</tbody>
</table>

Average oxytocinase activity of plasma obtained from pregnant women at different gestational ages. The activity corresponding to late pregnancy is adopted as 100 %.

(22) Oxytocinase. An enzyme which inactivates oxytocin appears during pregnancy in the blood plasma of women and some monkeys. The enzyme is also found in the pregnant myometrium and in the placenta where it is apparently produced (Carballo & Negréiros de Paiva 1960). In women the plasma concentration of oxytocinase increases with the gestational age (Table 2). Maxima are reached around the 36th week of pregnancy. No decline occurs prior to or during labour. After parturition the oxytocinase concentration decreases progressively, becoming undetectable in about one month (Semm 1960).

Plasma obtained from pregnant women near term, employed at 90 % concentration “in vitro” at 38°C, inactivates 50 % of added oxytocin in an average time of 4.5 minutes (Méndez-Bauer & Cabot 1960). This time interval is similar to the half life of oxytocin “in vivo” [See (13)].

The results obtained by Tuppy (1960) with biochemical methods are somewhat different from those obtained with biological methods.

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