Effects of Drugs on Uterine Contractility

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THE CURRENT trend in obstetrical management in labor and at delivery is one of tempered moderation, embodying the principles of individualization according to demonstrated needs and a critical consideration of the risks involved in administering drugs with regard to the potential impairment of fetal function and interference with the course of labor. As to the latter, because of the marked variability inherent in human labor and the difficulty in attaining critical objectivity, striking divergence of claims pertaining to the action of drugs on the course of labor appears throughout the medical literature. Findings are frequently reported indicating action of specific agents at either end of the spectrum with regard to inhibition or stimulation of uterine contractions. Not only are *in vivo* investigations at variance with those carried out *in vitro,* but animal studies differ considerably from each other and from observations in man. Alleged species specificity may explain these discrepancies, but it is more likely that distortions are due to inconsistencies in experimental conditions and control.

The physiology of uterine contractility and the course of labor in the human parturient has been studied in many ways, including clinical generalizations, comparing the duration of labor, evaluation of progression based on the pattern of cervical change, "pain counts," parturograms, external tokodynamometry, intra-amniotic, intramyometrial, and extraovular pressure measurements, electrohysterography, and more recently electrical resistive impedance plethysmography and electronic cervimetry. While much excellent work has been performed in pursuit of knowledge concerning uterine physiology, study of the individual variables has not given us a true picture of the overall "efficiency" of the complex machine with which we are dealing. Diminished uterine contractility in the form of shorter, less frequent, and/or less intense contractions, for example, may not be reflected in diminished rate of progressive cervical dilatation or descent of the fetal presenting part. There appears to be no single measure of overall performance which satisfies our desire for scientific objectivity. Nevertheless, a great deal of basic information is at hand, and it perhaps remains for the future to achieve total integration and rationalization of conflicting evidence.

A review of this type is necessarily incomplete in view of the enormous numbers of publications reporting upon myriads of compounds used during labor which potentially might influence uterine contractility. The prime objective here is to present documented effects and to delineate controversial issues concerning medications likely to be used in pregnancy and during labor.

Analgesic, Sedative, and Hypnotic Agents

The action of *morphine* on the isolated and intact uterus has been studied since the turn of the century. Opinions have been divided amongst those who felt they could demonstrate an inhibiting effect,[25, 38, 129] those who found a highly variable effect,[41, 111, 147] and those who showed no effect.[23, 48, 81, 156] The experimental approach in some of these reports was quite comparable despite the contradictory results obtained. This variation was explained, without supporting evidence, by Snyder[147] as possibly due to the uncovering of a deficiency of the expulsive uterine forces that might otherwise have been overlooked, under the influence of morphine. One may conjecture at length as to what the underlying problem might be.

The same contradictions exist with regard

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to the effect of *meperidine* on uterine contractility. Reports have described inhibition,[25, 97] variable responses,[38, 76] as well as no effect.[81, 147, 156] Discrepant experimental evidence notwithstanding, the overall clinical impression has been one of diminished uterine activity and progress. This is illustrated by the finding of significantly altered cervical dilatation-time patterns in labors where the patient had been heavily sedated.[53] Especially evident were the extreme prolongations which occurred when sedation was administered early in the first stage prior to active dilatation.[56] The difference in response of the uterus to sedation in the latent phase as contrasted with that of the active phase of the first stage (the former being considerably more sensitive) may offer a partial explanation for some of the differences encountered in experimental studies of contractility in labor. It is reasonable, for example, to expect major inhibition of uterine contractility when the narcotic agent is given early in the latent phase; but perhaps no effect at all during the active phase or second stage, unless the dosage is increased correspondingly.

Isolated reports of the influence of various narcotic-analgesics on myometrial function and the course of labor have indicated a variety of responses. *Heroin*, for example, was shown to have no appreciable effect.[147] *Methadone*, on the other hand, diminished uterine tone somewhat[38] when studied by various objective means. The course of labor appeared to be shortened in uncontrolled clinical studies of *oxymorphone*.[143, 146] *Alphaprodine* was demonstrated to have a variable action similar to meperidine[38] in objective experiments. Comparable variability was seen among patients given *phenazocine* during labor, studied on the basis of duration of labor.[32, 114, 134]

With regard to the *barbiturates*, there seems to be some uniformity of opinion indicating that large doses may seriously inhibit uterine contractility and slow the progress of clinical labor.[2, 25, 130, 156] The impairment in myometrial function appeared to be closely related to the dosage given. No effect was seen with minimal doses; diminished frequency and duration of contractions occurred with larger doses, and complete cessation of uterine activity took place with anesthetic doses.[147] This has been recorded with pentobarbital sodium[25, 130, 147, 156] and thiopental sodium.[2, 147] No inhibitory effect was seen with phenobarbital[156] in isolated human uterine muscle or with amobarbital[41] in labor studied by means of external hysterography.

Other agents such as *tribromoethanol* have been shown to prolong the interval between contractions, to delay labor even in low doses, and to produce marked uterine atony[41, 62] *Paraldehyde* appeared to be capable of prolonging labor and decreasing uterine activity, particularly after amnesic dosages.[65] The earlier it was given the longer and more persistent the effect, and the more difficult it was to overcome the inertia produced.[147]

The narcotic antagonists, *N-allylnormorphine* and *levallorphan*, have been shown[38] to act upon the uterus in a variable manner similar to that of meperidine, but to a lesser degree. No consistent diminution in depressing effect due to the action of narcotic-analgesic drugs on the uterus has been demonstrated by the use of the narcotic antagonists.

Ataractic Agents

Unsubstantiated and conflicting reports have appeared with regard to the effect on uterine contractility and the course of labor of the various tranquilizing drugs currently in wide use. There has been a discouraging dearth of controlled objective studies and simultaneously a deluge of clinical reports, many representing mere testimonials or at best less-than-ideally designed experiments. The evaluation of *promazine* on a clinical basis has shown a depressing effect,[14, 121] no effect,[107] and even an augmenting effect.[144, 149, 152] Objective investigations utilizing intrauterine pressure recording devices have also not been consistent, one study showing no effect[20] and another[169] demonstrating *in vitro* depression of spontaneous activity in proportion to the concentration, and *in vivo* diminution in amplitude and frequency of contractions. Progress in labor associated with the latter changes was found to be effectively halted during the 2 hours in which the drug was active.

Chlorpromazine appeared to prolong labor in several clinical studies,[26, 74, 136, 137] or to have no effect on labor,[75, 113] or even to shorten labor.[27, 68] Intra-amniotic pressure recordings showed no demonstrable effect from

chlorpromazine in 2 studies,[2, 24] and a depressant effect in 2 others [38, 160] as evidenced by diminished basal tonus and intensity, associated with progressive incoordination of the contractions. The recurrent complicating factor in these studies which present widely differing results was the concurrent administration of other sedative-analgesic medications, thereby confusing the issue. Repeatedly, it could be implied that concomitant diminution in the amount of sedative necessary for pain relief resulted secondarily in "improved" contractions. The confusion, insofar as evaluation of singular effect is concerned, is apparent.

Interpretation was particularly difficult when *promethazine* was used in labor. In 4 early clinical studies in which promethazine was studied in conjunction with other analgesic agents, it was concluded that labor was definitely and appreciably shortened.[26, 43, 63, 152] Each author stated independently or implied that the requirements for analgesic agents were diminished. The resultant labors were shorter than comparable labors in which the patients were given a greater quantity of analgesic drug. We have already alluded to the sensitivity of the uterus to sedative-analgesic drugs, particularly during the early latent phase of the first stage. There can be little doubt, therefore, that the resultant "shortening" was not necessarily due to the uterotonic activity of the tranquilizer used, but rather a secondary benefit due to the lesser amounts of narcotic required for pain relief. A single objective study, utilizing intrauterine amniotic fluid pressure catheter recordings throughout labor,[170] demonstrated the effects of promethazine to be characteristically that of inhibition of both the amplitude and frequency of the uterine contractions, without apparent influence on the resting tonus.

Because of the absence of objective studies, similar results were obtained with *perphenazine*. In studies taking into account only duration of labor and not adjusting for analgesic agents given simultaneously, perphenazine showed either no effect,[64] a slowing,[116] or an enhancing effect.[69, 152]

As to *prochlorperazine*, 2 uncontrolled clinical studies [84, 152] and 1 good *in vivo* experimental study [161] denied any real effect. The latter, an unusually well-controlled, objective experiment, showed that prochlorperazine delayed the patient's subjective awareness of uterine contraction, but had no apparent direct effect upon uterine contractility, either with regard to the mechanism of labor or its duration.

It is encouraging to see more objectivity in recent evaluations of *chlordiazepoxide* (Librium), as it affects uterine contractility. No response was seen in one tokographic study.[148] Marked relaxation which did not affect rhythmical contractility at low doses and still further relaxation with diminished frequency or cessation of spontaneous contraction at higher doses, was reported in an *in vitro* study.[9] No change at low doses, increased tone and contractile incoordination at moderate doses, and diminished resting tonus and spontaneous contractility at high doses were seen in an *in vivo* study using both internal and external tokography.[38] Unfortunately, therefore, despite objectivity the differences in the conditions of the several experiments are reflected in the variations in response obtained.

The antihistaminic *dimenhydrinate* (Dramamine) is included here because of its antiemetic and ataractic effects. Dimenhydrinate was alleged to shorten labor in one uncontrolled clinical study [138] and in one study [133] based on cervimetric data. In the former, apparent shortening occurred in patients who required lesser amounts of analgesic agent. In the latter, no correction was made for the differences that might be attributable to the analgesic potentiation of the test drug used. One well-designed, double-blind, clinical study [70] of dimenhydrinate demonstrated antihistaminic, atropine-like, local anesthetic and soporific effects, but no change in the duration of labor. The drug could not be demonstrated to have any uterotonic action.

Isolated reports have appeared on the effect on labor of a variety of related substances. *Hydroxydione* (Viadril), a corticosterone derivative with hypnotic and basal anesthetic actions, produced no appreciable change in intrauterine pressure patterns in the usual pharmacologic doses.[2] After prolonged use, however, diminished resting tonus and amplitude of contraction with increasing irregularity occurred. The tranquilizer *hydroxyzine hydrochloride* (Vistaril) did not affect the course

of the first stage of labor.[79] *Methotrimeprazine* (Levomepromazine), which has pharmacological effects similar to chlorpromazine, appeared to have a depressing effect similar to that of meperidine in a statistically well-designed, clinical study.[37] No effect on the course of labor or analgesic medication required was seen with the antidepressant, amine oxidase inhibitor, *nialamide* (Niamid), in a double-blind clinical study.[151] Recent data on the psychotropic drug, *diazepam* (Valium) showed no influence on tokographic patterns,[148] but a shorter labor relative to that in patients who received sedatives in addition.[60] Effects similar to this were encountered with the hypnotic, *ethchlorvynol* (Placidyl) in an uncontrolled study.[15]

Inhalation Agents

It is generally agreed that *nitrous oxide* has no effect on myometrial contractility. This is based both on clinical[65, 147] and experimental studies *in vivo*.[2, 20] Nevertheless, the latter are at variance with experiments using isolated human uterine muscle,[156] in which a depressant effect was encountered. Similarly, *ethylene* exhibited little or no influence on the course of labor.[65, 147] *Trichlorethylene* also showed no effect *in vivo*[2, 20] and *in vitro*.[156] One report,[50] however, indicated that prolonged use of trichlorethylene reduced the uterine contractile pattern.

There is unanimity of opinion concerning the effect of diethyl *ether* and divinyl ether anesthesia on the course of labor. The inhibitory effect has been well documented experimentally and clinically. Ether produced diminished tonus, amplitude, and frequency of uterine contractions, whether the contractions were spontaneous or induced by oxytocin.[2, 17, 20, 147] Contractions were abolished in the lower first or upper second plane of anesthesia.[162] The arrest of labor produced by ether anesthesia was apparently uninfluenced by uterotonic stimulation.[2] The latter finding verified experiments utilizing isolated gravid and nongravid uterine muscle strips.[156]

Similarly, definite inhibitory effects on uterine activity have been documented with *chloroform* in both clinical[42, 65, 109] and objective experiments.[20, 99, 147] Chloroform depressed uterine contractility in analgesic doses and in the first plane of anesthesia. Significant diminution of amplitude and frequency of contractions leading ultimately to complete relaxation, was found.

Cyclopropane, although depressing the activity of isolated uterine muscle strips,[156] has been shown in general to have no effect on the intact uterus in subanesthetic or light anesthetic (first plane) levels.[2, 20, 65, 109, 147] Deeper cyclopropane anesthesia, on the other hand, apparently will result in progressive decrease in the frequency of uterine contractions without significantly affecting the tonus or amplitude.[2] This agent, nevertheless, is of little value where complete relaxation of the uterus is required, as for intrauterine obstetrical manipulations.[109]

Halothane has been demonstrated to inhibit uterine contractions markedly and rapidly, even at light anesthetic levels. This has been shown both by internal [2] and by external[47] tokodynamometry. Complete obliteration of both spontaneous and oxytocin-induced contractions occurred. Halothane has been recommended as an agent of choice for treatment of tetanic uterine contractions[109, 110] because relaxation is prompt and complete. Unfortunately, severe postpartum atony uncontrolled by uterotonic agents has resulted as a consequence of the use of halothane.[153]

Conduction Anesthesia

As to the action of blocking agents on the motility of isolated human myometrium, direct local inhibition of contractile patterns has been elicited with procaine, tetracaine (Pontocaine), lidocaine (Xylocaine), chloroprocaine (Nesacaine), dibucaine (Nupercaine), hexylcaine (Cyclaine), and propoxycaine (Blockain).[103] However, the relatively small doses per unit weight employed clinically would appear insufficient to produce significant effects. Nevertheless, there are variations in the effect on labor according to the block techniques utilized in obstetrics.

Discrepancies exist in otherwise apparently reliable objective studies of the effect of *spinal* anesthesia on labor. In well-established labor, no consistent effect occurred with spinal anesthetic to the second thoracic level[3, 20] and even to sixth cervical level.[162] However, dis-

ruption of rate, rhythm, strength, and gradient of contractility with levels above the tenth thoracic have been reported.[17, 130] Indeed a well-documented study utilizing external hysterography [41] indicated that at lower anesthetic levels a significant rise in basal tonus occurred and persisted for about 45 minutes. This was accomplished by diminished frequency and amplitude of contractions for about 30 minutes after the anesthetic was given. All parameters subsequently returned to normal, the contractile pattern re-establishing itself even though anesthesia was maintained. Further confusion is contributed by studies [3, 20] which allude to striking improvement in some cases of incoordinate uterine dysfunction following administration of spinal anesthesia. Undoubtedly, factors other than the anesthetic agent and technique were at play. Among these, the type of labor pattern is important, perhaps more pertinently its temporal phase. It has been shown, for example, that spinal anesthesia given prior to the onset of the phase of dilatation in the first stage of labor will impede progress of the latent phase, and forestall the normal progressive changes of late labor.[56] It would seem that spinal block given after the latent phase has ended, in a patient whose labor is otherwise normal, and to a level which does not exceed that necessary for uterine pain relief (tenth thoracic) should not influence labor.

The general impression of *caudal* or *epidural* anesthesia as it affects labor is that of negligible influence, unless misused. Most clinical studies agree [16-18, 67, 147] that well-established labor is not retarded. This has been verified by objective studies utilizing intra-amniotic pressure,[2, 29, 162] external tokography,[130] and impedence plethysmography.[89] In other studies, nevertheless, it was found that anesthetic levels above tenth thoracic disrupted the contractility pattern [17, 130, 147] and impaired progress of labor.[55] On the basis of the reported studies,[2, 55] proper usage entails administration of this form of anesthesia after the active phase has been entered: if given earlier labor is delayed. The many reports of impairment of progress in the second stage, with inefficient flexion and rotation of the fetal presenting part, pertain more to diminished voluntary rectus muscle expulsive force, resulting from anesthetic abolition of the perineal reflex, than to the effect of myometrial function.

Paracervical block has been praised and deprecated for its ostensible effect on labor. Enhancement of cervical dilatation [35, 88, 115] as well as transient diminution in uterine contractility [135, 139] have been reported. The former may have been merely the rapidly advancing changes one should anticipate as labor progresses [53]; the latter, perhaps the result of the epinephrine administered simultaneously.[88, 119] Inhibition by epinephrine has been well documented (*vide infra*). Tokographic studies [31, 119] have shown no consistent uterine stimulation or depression as the result of paracervical block. The same results were obtained with *uterosacral* anesthesia.[119]

Pudendal nerve block did not interfere with uterine action,[65] although another report suggested a tendency to retard the second stage.[98] Combined paracervical and pudendal nerve block has been alleged to speed cervical dilatation, on the basis of uncontrolled clinical observations.[88] Paravertebral lumbar sympathetic block has been described as effective in promoting uterine contractility, with accompanying increase in resting tonus and amplitude of contractions, and a decrease in cervical resistance.[126, 127] Normal uterine contractions were apparently ameliorated and abnormal patterns corrected by this technique,[77] as shown by intra-amniotic pressure and external tokodynamometric studies.

Neuromuscular Blocking Agents

There has been no substantive evidence of action on the uterus of muscle relaxant drugs such as *d-tubocurarine, gallamine, decamethonium* or *suxamethonium*.[65, 71, 106, 150, 159, 165] One report suggested that labor is shortened,[52] another that the frequency and strength of contractions are depressed by profound curarization.[120] Nevertheless, it is generally held that not only are cervical dilatation and uterine contractility unaffected, but the uterine response to exogeneously administered uterotonic agents is likewise unaltered.[120, 150, 165] On the other hand, clinical impression to the contrary,[39] diminished intensity of uterine contraction has been reported with *succinylcholine* based on both subjective [4] and objective [38, 65] studies.

Antispasmodic Agents

The antispasmodic smooth muscle depressants and myovascular relaxant agents have a variable suppressing effect on uterine contractility. Clinical studies of the effect of *isoxsuprine* on labor have shown no effect,[12, 85] acceleration,[167] or an inhibiting effect.[11, 154] The latter was found especially in premature labor where the drug was used in attempts to arrest undesirable or untimely labor. Objective studies, *in vitro*,[82, 100] have demonstrated a depressant action of isoxuprine similar to but stronger than papavarine. Myometrial function was inhibited in the cat, rabbit, and dog.[100] In humans, uterine contractility was depressed at term.[73] This observation applied both to spontaneous and to oxytocin-induced contractions, although a variable response was encountered in premature labor.

Studies on isolated human myometrium [82] indicate that other antispasmodic agents depress the gravid uterine muscle. These include adiphenine (Trasentine), dicyclomine (Bentyl), valethamate (Murel), thiphenamil (Trocinate), and methylisooctenylamine (Octanil, Isometheptene). Still others, such as amyl nitrite, and nitroglycerine have no consistent effect.[81]

Steroid and Related Hormones

It is generally accepted that *estrogens* stimulate uterine contractions.[163] The potential capacity of the gravid uterus to contract requires priming with estrogenic substances.[20, 21] This observation is strengthened by animal and human experiments in which increase in spontaneous uterine activity, exemplified by more frequent contractions of greater amplitude, has been seen.[17, 111, 117, 118, 129] The contractions produced by estradiol are dissimilar to those produced by oxytocin, being shorter, of lower intensity, more frequent, less coordinated, and generally painless.[117] In addition, estrogens appear to reduce the threshold of myometrial responsiveness to oxytocin.[118] This may be a variable response, no effect being demonstrable in some studies.[81, 86] Indeed, estrogens actually have been found to block the contractile response to oxytocin of the rat myometrium, *in vitro*.[5]

A very interesting concept has been proposed by Shabanah and his co-workers [141, 142]—that estrogens control actomysin synthesis in the uterine myofibrils while assisting the synthesis of high energy phosphates (ATP) to provide the energy for actomysin contraction. Simultaneously, estrogens control synthesis and activation of acetylcholine and the resulting myometrial response. Furthermore, acetylcholine and compounds with acetylcholine-like activity stimulate the release of oxytocin, in turn the action of which on myometrium is only manifest in the presence of acetylcholine. Estrogens also control the synthesis of the catecholamines (*vide infra*). The myometrial response to the sympathetic neurohormonal transmitters is influenced by the level of progesterone. If these concepts are substantiated, the physiology of myometrial function will have been greatly clarified.

The myometrial response to *progesterone* is at best poorly understood.[163] In general, animal experimentation indicates that progesterone has a strong tendency to inhibit uterine contractility, to diminish spontaneous contractions and to overcome responsiveness to uterotonic agents.[5, 7, 21, 34, 57, 90, 91, 129] The evidence in man, however, has been contradictory. Although gestogens appear capable of preventing activity when hypertonic saline is used to induce abortions,[6] to inhibit spontaneous contractility *in vitro* in human myometrium,[19, 92] occasionally to reduce uterine activity in premature labor,[38] and to diminish spontaneous contractility at term,[17, 72, 163] the effects are inconsistent and not verified in other reports.[33, 86, 93, 123, 129, 157, 168] Intramyometrial injections of gestogens arrest some premature labors.[158] These discrepancies are explainable [163] by the difficulties inherent in the study of myometrial tissue, and by variations in technique and instrumentation from laboratory to laboratory.

Gonadotrophins may inactivate the rabbit myometrium although the evidence is indirect and inconclusive.[129] Similarly, *aldosterone* which has anti-progresterone effect, has been found to accentuate spontaneous uterine activity, thus annulling progesterone effect, when administered intravenously.[38]

Relaxin, a water soluble ovarian extract, not yet synthesized, is a source of debate with regard to myometrial function. Aside from its action, documented in lower animals, in re-

laxing the symphysis pubis and softening the cervix, the effect on myometrial activity has not been established. Reports indicating its ability to slow or terminate premature labor by inhibiting uterine contractions,[44, 51, 102, 105] to speed cervical dilatation,[10] or to shorten the first stage of labor [132] have not been verified. *In vitro* experiments utilizing isolated human uterine muscle have shown no effect.[104] Similarly, controlled clinical studies [36, 40, 80, 145, 164] and objective physiologic investigations [21, 87, 124] have uncovered no consistent inhibition or stimulation of uterine contractility.

Autonomic Blocking Agents

Among the postganglionic cholinergic blocking agents, the most commonly used in obstetrics are *atropine* and *scopolamine*. Although generally supposed not to have an effect on uterine activity [147] and to exert no significant influence on labor in normal situations,[62, 140] these drugs exhibit an antispasmodic action. By means of intra-amniotic pressure studies [38, 62] both drugs have been shown to relax the lower uterine segment somewhat, and to diminish basal tonus and frequency of contractions. Furthermore, regulation of uterine activity in incoordinate states has been observed. In the excised uterus, the circular but not the longitudinal fibers are relaxed by atropine.[62] In clinical usage, nevertheless, the effect of these drugs appears to be negligible.

Among the adrenergic blocking agents, perhaps the most widely used in obstetrics are the *ergot alkaloids* and their derivatives. These substances have been used for their uterotonic activity since introduction into practice at the beginning of the nineteenth century. In obstetrical practice today, use is limited to the postpartum period because of the intensity of unphysiologic contractions produced during labor. The amine alkaloids, such as *ergonovine* and the semisynthetic *methylergonovine,* are effective oxytocic agents with rapid onset of action, and negligible adrenergic activity. They are effective orally as well as parenterally. The dihydrogenated alkaloids, on the other hand, are essentially inactive insofar as uterine contractility is concerned, but have a greater adrenergic effect than the naturally occurring amino acid alkaloids from which they are derived. *Dihydroergotamine* has been said to raise the basal tonus,[38] to have no effect upon the uterus,[61, 81] to increase the tonus and frequency of contractions but reduce the intensity,[22, 140] or produce uterine atony in the third stage of labor.[54]

Large doses of the more potent adrenergic blocking agents, *dibenamine* and *dibenzyline* have no direct effect on uterine muscle.[62] The imidazolines, *tolazoline* (Priscoline) and *phentolamine* (regitine) on the other hand, apparently stimulate the uterus directly *in vivo* and *in vitro* in many species.[62] Although these agents should be expected to act the same way in humans, the effect on uterotonic activity has not been reported. Similarly, the benzodioxans, *piperoxan* and *prosympal,* directly stimulate the smooth muscle of the uterus.[62]

Nicotine of all the ganglionic blocking agents is perhaps the most widely prevalent. Aside from fairly good documentation of the association between smoking and low infant body weight,[128] the expected stimulation of uterine activity has been observed *in vivo* but not *in vitro*.[94] A confirmatory study [101] alludes to the diminished need for surgical induction of labor among mothers who smoke. Whether the potential uterotonic action is due to direct stimulation or to the release of oxytocin by a nicotinic effect on the neurohypophysis, as demonstrated in rats,[13] has not yet been clarified in man.

Nicotinic properties have been ascribed to the quaternary ammonium compounds, notably the *tetraethylammonium* ion. Although largely replaced by hexamethonium as a therapeutic autonomic ganglionic blocking agent, it has been shown to be mildly uterotonic, improving contractility especially in incoordinate dysfunctional labor.[81]

Among the parasympathomimetic agents in current common use, the choline ester, *acetylcholine,* is of limited clinical interest largely because of its pharmacologic instability. Nevertheless, acetylcholine in large doses produces a good uterine response in the intact gravid uterus.[142] In smaller doses this effect was not seen.[46, 140] It has been asserted [141] that myometrial responsiveness to oxytocin will be manifest only in the presence of acetylcholine. The synthetic choline derivative *carbachol* has been shown to have the same effect as acetylcholine.[142] The cholinesterase inhibitors,

which prevent the destruction of acetylcholine, should be expected to yield an effect upon the uterus similar to that of acetylcholine. Nevertheless, the uterus is apparently not affected by *physostigmine*, except in high concentrations.[62] This is explained by the lack of continuous release of acetylcholine in the uterus; thus the myometrium will not be stimulated by a drug which acts through inhibition of cholinesterase. Similarly, *neostigmine* does not stimulate the pregnant uterus, except at term.[62] Because of its effect in correcting deficiencies in premenstrual uterine hyperemia, its ability to correct delayed anovulatory menstruation (once deemed useful in the diagnosis of early pregnancy), neostigmine has been stigmatized mistakenly as an abortifacient. Although not completely vindicated, the danger of neostigmine inducing abortion is unlikely. Among the cholinergic alkaloids, *pilocarpine* has been shown to produce uterine contractions in the uterus primed by estrogens.[129]

Paradoxical effects have been obtained with the sympathomimetic agents. In general it may be stated that *epinephrine* inhibits contractility of the pregnant uterus, while *norepinephrine* is a stimulant. Earlier work using impure commercial admixtures of adrenalin, containing roughly 80 per cent epinephrine and 20 per cent norepinephrine, produced confusing and often contradictory results. Thus, tokographic studies showed stimulation of uterine activity with high doses and inhibition with lower doses.[17, 83, 130, 140] With purification of the active principles and more critical studies, it was clearly established that diminution in frequency and amplitude of contractions occur following the administration of epinephrine *in vitro* [30] and *in vivo*.[21, 59, 122, 131, 155, 171] Basal tonus appeared to remain constant.[21, 59] Rebound of uterine activity followed, but not invariably.[21, 83, 122] This action was seen to affect both spontaneous and oxytocin-induced uterine contractions.[122, 171] Norepinephrine, on the other hand, initiated spontaneous contractions *in vitro* [30] and augmented uterine activity *in vivo* by increasing the frequency and amplitude of contractions.[21, 28, 59] The contractions produced by norepinephrine, however, led to incoordinate activity in many instances.[28, 171] The contractions produced differed both qualitatively and quantitatively from those produced by oxytocin.[28]

Quite pertinently, Reynolds [129] has rationalized that many of the paradoxical effects of drugs on the uterus might be explained by the probability that some exert their action directly while others, not in themselves adrenergic, indirectly excite the uterus by cholinergic nervous activity. Consequently, a sympathomimetic effect upon the uterus is indirectly obtained. Such an observation may well be valid, but in our present state of limited knowledge with regard to the interrelationship of neural and hormonal functions and the control of myometrial activity, it cannot be verified.

Miscellaneous Agents

Early clinical work [81] and experimental observations [1, 125] on *magnesium sulphate* indicated a limited or negligible effect in labor. These studies apparently did not take into account circulating blood levels. Recent critical evaluations [66, 95, 156] have clearly demonstrated the inhibitory effect of magnesium ion on the spontaneous contractility of the isolated gravid and non-gravid uterine muscle, resulting in diminution of intensity, frequency, and tonus. *In-vivo* studies [66, 78, 95] have also shown depression of uterine activity proportional to the level of magnesium ion in the blood. Suppression of activity was seen mostly in the effect on frequency of contractions,[95] but intensity and resting tonus were also affected variably [78] and the duration of labor prolonged.[66]

Enigmatically, *histamine*, although stimulating uterine muscle by direct action,[62] has been shown to lack uterotonic effect in low dosage during pregnancy.[108] The antihistamines, on the other hand, are in general, mildly spasmogenic insofar as myometrial contractility is concerned.[62] The lack of a clearcut effect from dimenhydrinate has already been mentioned.

Intravenous *ethyl alcohol* analgesia has been shown to slow or stop normal spontaneous labor, and temporarily to relax the tetanically contracted uterus.[49] Oxytocin-induced labor appears to be unaffected by alcohol infusion.[166] One report indicates that alcohol inhibits the release of oxytocin from the pituitary gland.[58]

Using animal and human myometrium from pregnant and nonpregnant uteri, *digoxin* has been shown to cause an increase in frequency

of contraction with failure of complete relaxation between contractions.[112] The same results were obtained with *ouabain* and *strophanthin G, in vivo.* Clinical labor, however, was unaffected.[112] It has been conjectured that the uterotonic effect of the cardiac glycosides may be functionally related to the pharmacologic uterotonic action of sparteine sulphate.

Bradykinin has been shown to exert an inconsistent uterotonic action on the isolated rat uterus [45] but no effect on the intact human uterus.[8] Nevertheless, this drug has a dilator action on smooth muscle, effectively blocks both spontaneous and oxytocin-induced contractions of human uterine muscle strips and decreases the frequency and amplitude of contraction of both gravid and nongravid muscle.[96] The degree of relaxation induced by bradykinin is proportional to the dose. These initial reports indicate the need for further study.

Conclusion

More questions have been raised than answered by this admittedly general review of the effects of commonly utilized drugs on uterine contractility. Our current state of ignorance with regard to basic uterine physiology has been clearly illustrated in this survey. Controversies exist in many quarters and await resolution by refined objective techniques of study, under ideally designed experimental conditions. It is anticipated that with the development of more critical approaches to the investigation of complex labor phenomena and the intercorrelation of data derived from meaningful experiments, the physiology of the pregnant uterus and the pharmacologic effects of exogenously administered agents will be elucidated.

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EPIDURAL-SUBARACHNOID Effects of a high subarachnoid block and high epidural block, with and without epinephrine in the anesthetic solution, were studied in the same patients. High subarachnoid block produces hypotension, decreased stroke volume, decreased cardiac output, and a slight decrease in total peripheral resistance. High epidural block with epinephrine in the anesthetic solution produces the same degree of hypotension, but an increase in heart rate, stroke volume, and cardiac output and a marked drop in peripheral resistance. High epidural block without epinephrine produces changes similar to, but not as profound as, subarachnoid anesthesia. Unmedicated patients blocked by high subarachnoid anesthesia hyperventilate and maintain normal blood gas tensions. The marked differences between effects of subarachnoid block and those of epidural block with epinephrine are explained by absorption of epinephrine into the systemic circulation of the latter group. This produces a beta-response to epinephrine, *viz.*, vasodilatation and cardiac stimulation, with resultant lowering of total peripheral resistance, increase in heart rate and stroke volume. (*Ward, R. J., and others: Epidural and Subarachnoid Anesthesia, J.A.M.A. 191: 275 (Jan. 25) 1965.*)