responding patch. In the absence of propagation, action potentials of perfectly graded height can be produced (ref. 3). It will be noted in ref. 1*f*, Fig. 2, that in the presence of the 4-megohm shunt across the second gap, action potentials appearing after long utilization time were no longer elicited and that the brief action potentials were followed by the R_1 deflection until the applied current became large enough to reduce the effectiveness of the R_1 process. The transition from record *11* to record *12* (1*f*, Fig. 2) was all-or-nothing. However, as will be illustrated in a future communication, in the presence of a low-resistance shunt across the second gap the height of the action potential may be perfectly graded from zero up to maximal.

[3] (*a*) Honrubia, V., and R. Lorente de Nó, these PROCEEDINGS, **48**, 2065 (1962); (*b*) *ibid.*, **49**, 40 (1963). The texts of these communications remain fully valid if the term "node" is replaced by "responding paranodal segment," because under the experimental conditions that were used, either only one paranodal segment is able to produce an action potential or if both paranodal segments respond to the stimulating current, they do so almost simultaneously.

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*THE EFFECT OF PROGESTERONE ON THE HUMAN UTERUS**

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Soon after Corner and Allen's discovery[1] of progesterone and the unique effect of this steroid on the maintenance of pregnancy in the rabbit, the question arose whether this hormone has a general role in regulating myometrial function in mammals and man. Recently the opinion[2] has been expressed that progesterone has no effect on the human myometrium and that profound differences exist among various species in the regulation of uterine function in the maintenance and termination of pregnancy. This concept discouraged the search for a basic regulatory mechanism common to different species. It also encouraged the thought that superimposed modifications of this basic mechanism in different animals and man represent alternative mechanisms for the control of uterine activity.

The debate was kept open, however, by the discovery of the progesterone *block*[3] and by the proposal[4] that two extreme species, humans and rabbits, do not differ in their basic mechanism of uterine regulation, but in the relative contributions to the myometrial block of a local placental and a systemic ovarian progesterone effect.

This view was not generally accepted. Endocrinologists insisted that the "progesterone theory"[4–6] is proved by the demonstration of a coincidence between progesterone withdrawal in the peripheral blood and the onset of labor. Clinicians, ourselves included, demanded proof that progesterone therapy extinguishes uterine activity and response to oxytocin and thus prolongs pregnancy. These demands were not fully justified, for in the progesterone theory a correlation was only predicted between myometrial progesterone concentration, the blocking effect, the character and magnitude of uterine activity, and clinical conditions. Furthermore, the theory[7] of the "local" effect of placental progesterone stated explicitly that the endocrine and functional asymmetry of the human uterus may not be readily modified by systemic progesterone treatment, nor reflected by peripheral blood progesterone levels.

Clinical trials of others,[8, 9] as well as our own,[10, 11] showed that the progesterone effect is variable during spontaneous and induced labor. Some investigators failed completely to demonstrate a progesterone effect.[12, 13] These studies remained controversial, the more so since uterine activity in early labor is variable and may diminish spontaneously. Partial obstruction of the recording catheter may imitate the progesterone effect, and the published records cannot be interpreted when only small fragments of the original tracings are presented.

Yet under this debate lies a crucial issue. The question is whether or not a profound species difference exists in myometrial function and regulation in the progesterone block and in the mechanism which controls the uterus during the menstrual cycle, pregnancy, and parturition. Since final evidence for a fundamental similarity in these biological processes in all mammals can only be provided after very considerable technical and conceptual advances, specifically in biophysics and steroid chemistry, it seems advisable to attack at present those problems which may yield to available methods.

The progesterone theory[4–7] implies that the myometrial block should be similar in rabbits and nonpregnant women, irrespective of whether the hormone is supplied by the ovaries or by therapy, for in nonpregnant women progesterone is supplied to the uterus from the ovary systemically, as in rabbits, whereas in human pregnancy it is presumably supplied locally by the placenta. The verification of this prediction requires only an accurate method for recording the intrauterine pressure. Such a technique has been developed recently.[14]

Study of cyclic uterine activity in nonpregnant women with this method revealed two significant facts. (1) During the menstrual flow uterine activity is not only very marked (in fact greater than during parturition) but it is relatively regular, propagating, and therefore synchronous throughout the organ like the activity of the rabbit uterus in natural estrus. (2) For about 14 days, starting shortly before ovulation, uterine activity is local, nonpropagating, and thus minimal; and the oxytocin response is extinguished. The human uterus during this period has the character of a blocked muscle, like the rabbit uterus after ovulation.

The present experiments were designed to establish the blocking effect of progesterone on the nonpregnant human uterus. Knowing that during the menstrual flow the intrauterine pressure is excessive, relatively regular, and constant, and that the organ is apparently free from the influence of progesterone, the studies were carried out during the first days of the menstrual cycle. The question was whether or not excessive, propagating, synchronous uterine activity can be changed to partly propagating, asynchronous, or local activity by progesterone therapy and whether the oxytocin response can be reduced. A positive answer was anticipated on the basis of earlier experiments in rabbits[3–6] and of experiences with the human uterus at midcycle,[14] when local activity and lack of oxytocin response coincide with the secretion of progesterone by the preovulatory follicle and the corpus luteum.

Figure 1 illustrates the characteristic cyclic uterine activity of a patient during a complete menstrual cycle. This control run preceding a test of progesterone action shows that shortly before and after ovulation uterine activity is local and nonpropagating, and the oxytocin response is abolished as it is in rabbits after ovulation or progesterone treatment.

Figures 2*A* and 2*B* illustrate the effect of progesterone on the human uterus.

Following progesterone injection both the character and magnitude of the intrauterine pressure is gradually altered. The amplitude and frequency are reduced. The shape of the pressure curves gradually become irregular, and the rate of rise in pressure is decreased. The effect is still marked about 24 hr after treatment. These

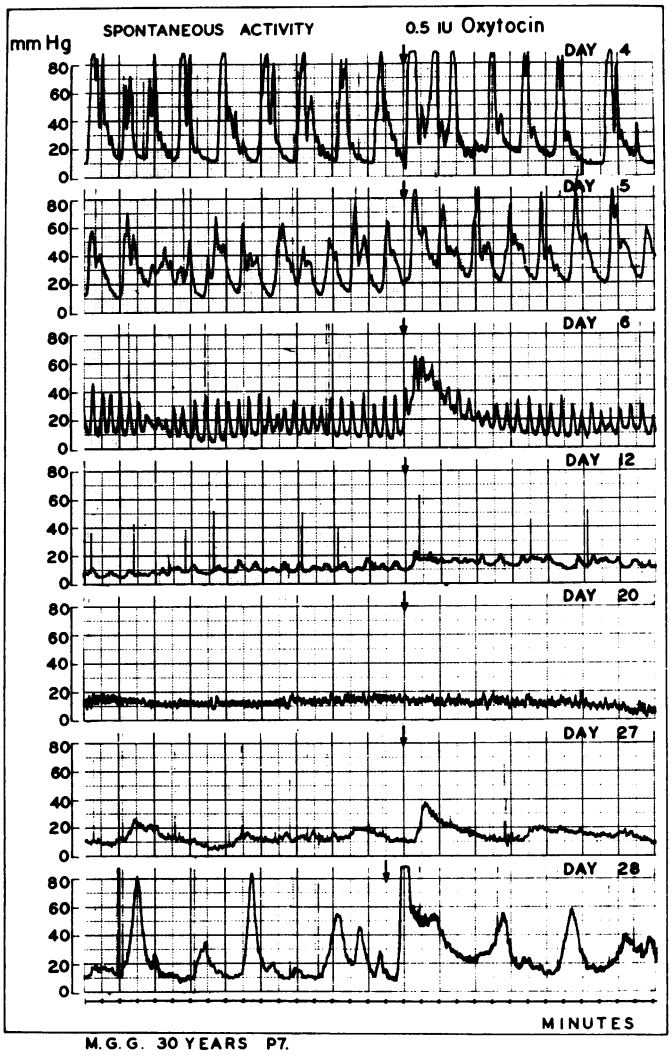


FIG. 1.—Cyclic activity of the myometrium during the menstrual cycle. All records are original tracings obtained during one menstrual cycle in the same patient. Note the extreme, propagating activity and marked oxytocin response during the menstrual flow, the local nonpropagating activity and the lack of oxytocin response shortly before and after ovulation, and the partly propagating activity and reduced oxytocin response during transition between these two extreme conditions of the myometrium.

changes are characteristic of a blocking action; propagating, synchronous activity changes to partly propagating asynchronous activity.

The reversibility of the progesterone effect was evident on day 6 (Fig. 2*B*), when activity fully returned to the pattern of day 4 (Fig. 2*A*). The repeatability of the effect was then studied by giving the same patient a second injection of proges-

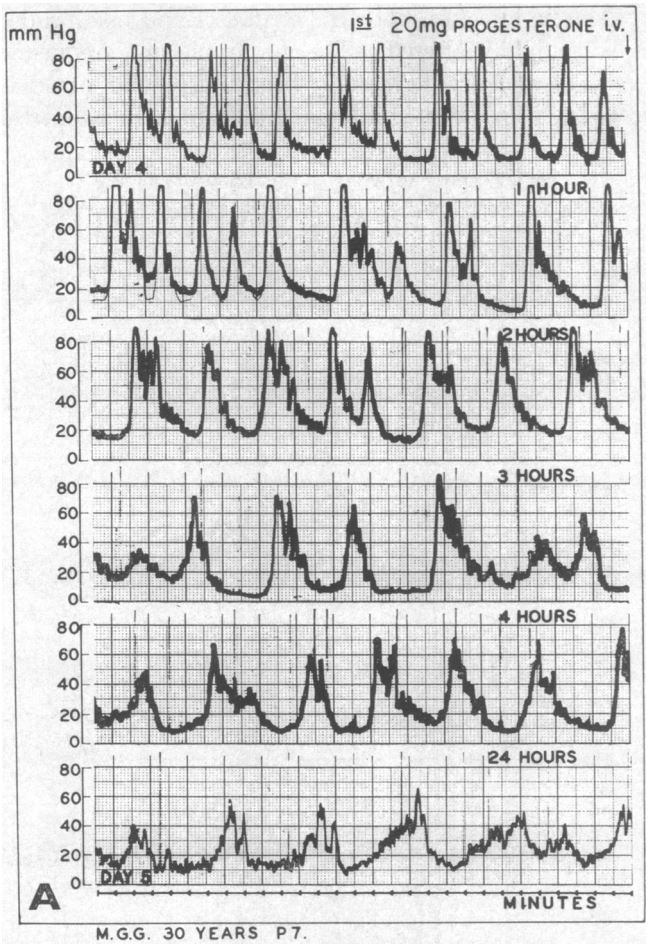
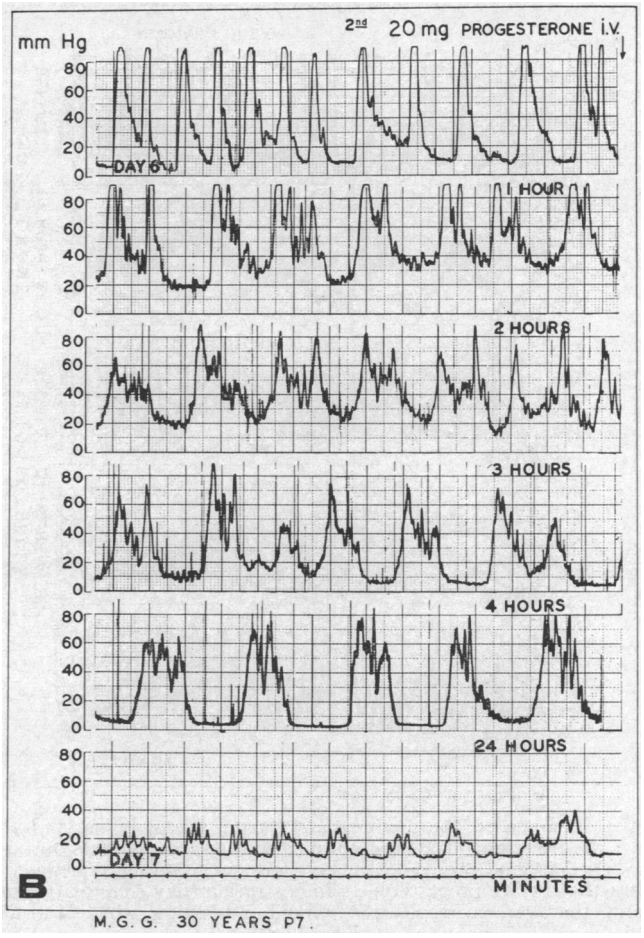


FIG. 2.—Effect of intravenous progesterone on the nonpregnant human uterus. All records are original tracings obtained in the same patient during days 4–7 of the menstrual cycle. Progesterone was administered intravenously on days 4 and 6, 20 mg each time. The development and withdrawal of the effect was determined by recording the intrauterine pressure repeatedly. Note the extreme, propagating, synchronous activity before progesterone administration (day 4)

terone. Figure 2*B* illustrates the good repeatability of the effect. Records from the same patient at day 8 showed that her uterus recovered also from the second progesterone effect.

During this study, marked changes were also observed in the oxytocin response of the uterus. Single intravenous oxytocin injections of 0.5 I.U. were given both before progesterone treatment and after the uterus recovered from the progesterone effect (i.e., days 4, 6, and 8), as well as when the progesterone effect was manifest (i.e., days 5 and 7). Figure 3 documents that progesterone treatment reduces the oxytocin response of the human uterus.

Figure 4 illustrates the changes in the rate of rise in pressure during the development of the progesterone action and during recovery from the progesterone block. The rate of rise in pressure, shown by high-speed recording, slows down as the block develops and is then accelerated as the



(*Fig. 2, cont'd*)
and after recovery from the blocking effect (day 6), and the local, asynchronous activity during the progesterone block (days 5 and 7). Note also the intermediate condition of partly propagating activity during the gradual development of the block (1–4 hr after progesterone administration). Note the good repeatability of the effect by comparing the 2 sets of tracings.

block weakens. Clearly, at a given time during the contraction phase, only a part of the organ is active, either because propagation is limited or because the propagation velocity is reduced. In either case a considerable portion of the organ remains inactive when the contractile system of the pacemaker area and of the nearby regions is activated. The inactive area must be stretched by the actively shortening region before the organ as a whole can develop active pressure. The result is that the rate of rise in pressure is reduced.

Figure 5 illustrates the characteristic effect on the nonpregnant human uterus of 500 mg progesterone, injected intramuscularly in oil. Here, as before, is evidence that the excessive, propagating activity and oxytocin response of the nonpregnant human uterus are drastically modified by progesterone therapy. Already at 3–6 hr following treatment, activity is local, nonpropagating, and the oxytocin response is reduced. The effect is still apparent 24 hr after treatment.

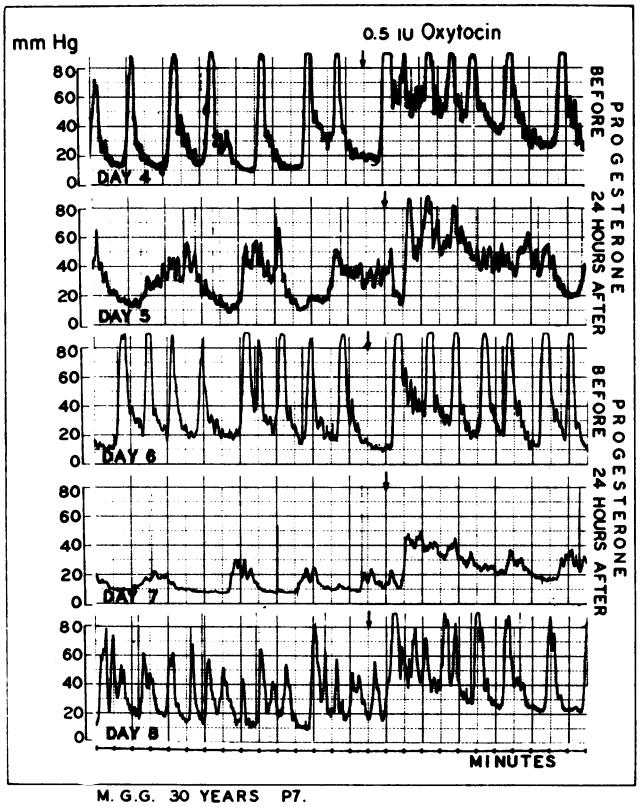


FIG. 3.—Effect of oxytocin on the nonpregnant human uterus before and after progesterone treatment. All records are original tracings obtained in the same patients during days 4–8 of the menstrual cycle. The patients received 2 intravenous progesterone injections, 20 mg each, on days 4 and 6. Note that before progesterone administration (day 4) and after recovery from the block (days 6 and 8) the oxytocin response is marked and lasting, while 24 hr after progesterone treatment (days 5 and 7) it is slight and of short duration.

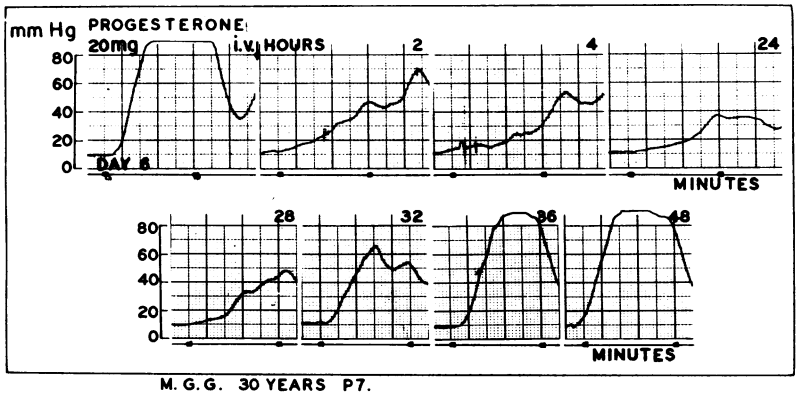


FIG. 4.—Effect of progesterone on the rate of pressure rise in the nonpregnant human uterus. All records are original tracings obtained in the same patient (through high-speed recording) during the gradual development of the progesterone block and during recovery from the block. The patient received intravenously 20 mg progesterone after the control run. Note the smooth, rapid, and quadratic rise in the intrauterine pressure before progesterone administration and after recovery. Note the irregular, slow, mostly linear rise during the progesterone effect.

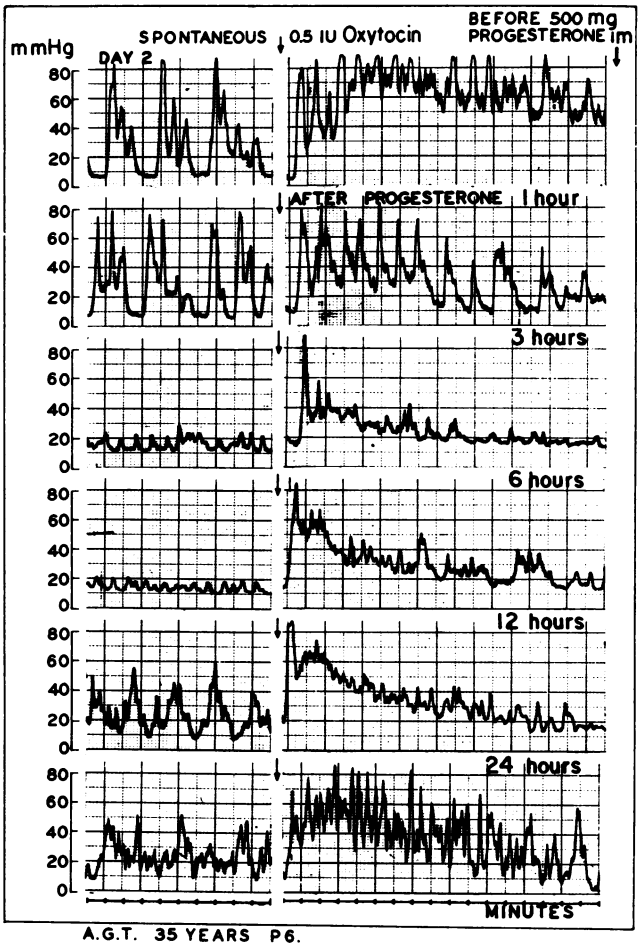


FIG. 5.—Effect of intramuscular progesterone on the nonpregnant human uterus. All records are original tracings obtained in the same patient before and after the intramuscular injection of 500 mg progesterone, in oil. Note the changes in spontaneous activity and oxytocin response (as a function of time) after progesterone administration. Propagating activity changes gradually to local activity, and the oxytocin response is reduced. Note also partial recovery 12–24 hr after treatment.

Unlike the late pregnant or parturient human uterus, the nonpregnant myometrium responds to progesterone predictably, by undergoing a block similar to that demonstrated in rabbits. It would seem, therefore, that in the absence of an intrauterine progesterone source—the placenta—as a complicating factor, the human uterus responds to systemic progesterone therapy as predicted by the progesterone theory.[4–7] Thus the idea[2] of a profound species difference between rabbits and women in the mechanism of myometrial function and regulation must be abandoned. Efforts to repeat, on the human uterus, original observations on laboratory animals, must continue but the results of these investigations should be placed in proper perspective. By considering the significance of the progesterone block in regulating the human uterus in various reproductive conditions, we may learn about the mode of action of contraceptive devices, the relative hazards of the prolonged use of the different

devices, the mechanism of the maintenance and termination of pregnancy, and about functional myometrial disorders. The common basic regulatory mechanism of the myometrium must be thoroughly investigated before evaluating the importance of superimposed modifications. The recognition that it is fundamentally alike in the various mammalian species promises to provide order in an important field of reproductive biology where controversy and confusion have prevailed.

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*ROLE OF RIBOSOMES IN STREPTOMYCIN-ACTIVATED SUPPRESSION**

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It is known[1, 2] that when a streptomycin-resistant (Sm^R) mutation is imposed on a Sm-sensitive (Sm^S) strain bearing a Sm-suppressible (SSu) defect, i.e., an impairment phenotypically corrected by Sm, two types of mutants are obtained: one remains correctable by Sm (conditionally Sm-dependent phenotype = CSD), and the other does not (defective phenotype). Two Sm^R alleles, competent and incompetent, are thus recognizable on the basis of their ability to permit Sm-suppression of a given SSu defect; their ratio depends on the parent strain. Furthermore, some competent mutants were always found among the auxotrophs derived from every randomly chosen Sm^R parent so far tested. It therefore appears unlikely that Sm^R mutations exist which are absolutely incompetent, i.e., are unable to per-