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THE ACTION OF PITUITARY EXTRACT UPON THE PREGNANT UTERUS OF THE RABBIT.

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Dixon and Marshall(1) have recently shown the existence of a relation between the cyclic activity of the ovary and the pituitary gland. They state that the pituitary gland secretes into the cerebro-spinal fluid, and that the amount of secretion depends largely upon whether corpora lutea are absent or present; that is to say, the secretion of the ovary in the absence of fully formed corpora lutea has a specific stimulating effect in promoting pituitary secretion. Finally, they came to the conclusion that, as the corpus luteum is supposed to undergo retrogression shortly before the close of pregnancy, the revival of the ovarian secretion causes a sudden increase of pituitary secretion, which, by its action on the more irritable uterine muscle, brings about labour. Thus, it is the increase of the pituitary secretion that is looked upon as an important factor in starting parturition.

Approximately at the same time Clark and Knaus(2) studied the conduction of contractions in the uterine muscle, and found that distinct changes in the mechanism of this muscle take place in the different stages of the œstrous cycle. The experiments were carried out on the isolated rat's uterus, and the tracings were obtained by recording simultaneously the contraction of three parts of the organ, namely, the vaginal, the middle and the ovarian parts.

It was found that in the dicestrous period there is a slow conduction between the ovarian and the middle part of the uterus, and that the vaginal part contracts independently of the other two.

A remarkable change takes place under the action of pituitary. All three parts of the muscle now contract practically simultaneously, just as they do in the normal uterus at œstrus or in early pregnancy.

It seems that pituitary has induced the same effect in the uterus at the dicestrous period as that which occurs naturally at œstrus and during early pregnancy.

These two independent observations suggested that the change of

the mechanism in the uterine muscle that occurred from the dicestrous period to œstrus and pregnancy might be due to an increase of pituitary secretion during the latter periods. That is to say, the changes here described in the behaviour of the uterine muscle from period to period might be due only to a varying increase and decrease of pituitary secretion; and in pregnancy they would be due to a steady increase, or even as Dixon and Marshall suggest, to a sudden increase of pituitary secretion at the end of pregnancy, finally bringing about labour. If this should be so then it seemed reasonable to assume that it might be possible, by creating these conditions artificially, that is, by injecting an appropriate quantity of pituitary into the body of the animal, to induce parturition at any time of pregnancy.

For this purpose it was necessary to keep the animal under an even influence of pituitary throughout a spell of 10 hours or so, in order thereby to create conditions similar to those which occur naturally at the end of pregnancy. It has been shown by the author elsewhere (7) that a small quantity of pituitary extract (equal to 1 mgrm. of moist posterior lobe), when injected intravenously into a cat, produces a marked effect on the uterus lasting for at least an hour. This indicated a method for keeping the animal under the prolonged action of a known quantity of pituitary by injecting the drug intravenously at hourly intervals.

Because of two obvious advantages the rabbit was chosen for this investigation. First, the rabbit's ear-veins offer the greatest possible convenience for repeated injections without injury to the animal. Secondly, if the doe is in good condition, she never ceases to breed, which consequently allows the investigation to be continued without interruption. Besides, the rabbit may be mated at any time during a prolonged heat, and, as the act of successful copulation is quite definite, the precise time at which pregnancy starts can be fixed. Thus, as one can always know the exact day of pregnancy of any doe, and, as the duration of pregnancy (namely 31–32 days) is fairly regular in any one strain of rabbits, the experiments can be repeated under almost identical conditions, on any particular day of pregnancy.

It was considered best to start with does at the end of pregnancy, to continue by working backwards in stages of pregnancy day by day, and to conclude on does at the very beginning of pregnancy. The reason for so doing was to ascertain, first of all, the minimum quantity of pituitary strong enough to induce parturition on the last day of gestation. In the case of the cat, already referred to, it was found that a dose of pituitary extract equal to 0·004 mgrm. of moist posterior lobe per kilo cat is the

minimum that produces a visible effect on the uterus *in situ*. This minimum amount was therefore taken as the starting-point. The extract used was that of Parke, Davis and Co., which the author has recently standardised after the method suggested by Burn and Dale (9), and has estimated to be equal to 30 mgrm. of moist gland per 1 c.c.

The results obtained may be divided into three groups, namely, those concerning the time: (1) from the 32nd backwards to the 29th day of pregnancy, (2) from the 28th to the 18th day of pregnancy, and (3) from the 17th to the 1st day of pregnancy. They will now be described in the order in which they were actually worked out.

Group 1. *Covering the time from the* 32*nd backwards to the* 29*th day of pregnancy.*

That the does were not under actual labour at the time when the injections were commenced was taken for granted because of the fact that they had not yet made a fur-nest, as they normally do some short time before they produce their young. Furthermore, to ensure that the injection itself was not the cause of the onset of labour, from mechanical or other causes, control injections with saline solution were given without causing any visible effect. Thus, it was made certain that all the occurrences following the pituitary injections were really the result of the drug administered. In all the cases of this group immediate delivery of live fœtuses could be induced by injecting a certain quantity of pituitary.

The facts concerning the 32nd and 31st days of pregnancy will first be dealt with, as these results are more or less equivalent to each other, owing probably to slight variations in the length of pregnancy. The smallest quantity of pituitary needed to cause immediate parturition was equal to 0·0075 mgrm. of moist posterior lobe per kilo rabbit. As a rule, the does showed distinct signs of straining immediately after the administration of the pituitary, and cast the first of their young within 1–3 minutes afterwards. The action of this very small quantity of pituitary was just sufficient to give the uterus power to get rid of one fœtus, and no more. When, after an interval of 4–6 hours, a second injection of the same minute dose of pituitary was administered, the second fœtus was born, and so on, showing that the pituitary action was so slight and short in duration that it was exhausted with the delivery of a single fœtus. When the dose of pituitary was increased to an amount 10–20 times as large as the minimum quantity a different thing happened, namely, one fœtus after another was cast, so that within 5–10 minutes

the whole litter was born. At a normal birth the young rabbit is born enclosed in the fœtal membranes and placenta, so that the whole ovum is cast *in toto*; under the action of pituitary the young, especially the first one, were very often born without the placenta, which usually followed a short time afterwards, sometimes as a result of a second injection.

The results obtained on the 30th day of pregnancy did not differ in nature from those described above; but for inducing parturition on this day a much larger quantity of pituitary was required than on the last two days of pregnancy, namely, a dose equal to 0·3 mgrm. of moist gland. With the increase of the dose of pituitary there was an obvious delay in the response, as the actual birth occurred usually only after prolonged treatment extending over several hours.

On the 29th day of pregnancy a further increase of pituitary was needed in order to obtain the same result as on the last three days of gestation. The minimum quantity was found to be equal to 0·6 mgrm. of moist gland per kilo rabbit and the number of injections required to produce birth varied between one and eight. On this day in particular it very often happened that the response of the uterus to the pituitary injection was the delivery of one young only; for example, one doe was given three injections of pituitary at hourly intervals; 5 minutes after the third injection one fœtus, looking very underdeveloped, yet alive, was cast without the placenta. No more injections were given on this day, but three days afterwards, on the 32nd day of pregnancy (the normal duration), another nine fully developed young were born, these averaging 20 grm. heavier than the one produced by the action of pituitary on the 29th day.

In short, it was possible to induce parturition by injecting a certain quantity of pituitary on the 32nd, 31st, 30th and 29th day of pregnancy. The minimum dose of pituitary strong enough to cause delivery on the 32nd and 31st day appeared to be equal to 0·0075 mgrm. of moist gland per kilo rabbit, rising to 0·3 mgrm. on the 30th day, and to 0·6 mgrm. on the 29th day of pregnancy. The complete delivery of the litter could always be induced, and this depended only on the amount of pituitary injected.

Group 2. *Covering the time from the* 28*th to the* 18*th day of pregnancy.*

In all experiments of this group the does were given nine injections of pituitary at hourly intervals, so that they were kept under continual pituitary action throughout 9 hours. It may be said at once that this

period is characterised by the fact that no quantity of pituitary was ever found sufficient to induce abortion during the day on which the experiment was carried out. As a result of this prolonged pituitary action, however, the fœtuses were killed inside the uterus, and were cast some days subsequently. After this fact had been established, the next step was to find out approximately the minimum quantity of pituitary sufficient to cause the death of the fœtuses on the various days of this period. It was found that a dose of pituitary extract equal to 1·3 mgrm. of moist gland per kilo rabbit administered for every injection on the 28th day of pregnancy, a dose equal to 1·5 mgrm. of moist gland administered on the 27th day, and a dose equal to 2 mgrm. of moist gland given on all the other days back to the 18th day of pregnancy, was succeeded by abortion some days subsequently. The interval between the injections and the subsequent abortion varied from 2–6 days. In some cases, in which the experiment was performed on the 26th and 27th days of pregnancy, abortion occurred at the normal end of pregnancy, namely on the 32nd day. That the fœtuses had died in these cases in consequence of the pituitary action seemed to be proved by their appearance, in that they were distinctly underdeveloped, the stage of development varying with the day of pregnancy on which the injections had been made, and were far lighter in weight than the average young born normally. In some cases, however, one or two young escaped death and were born alive amidst the emaciated mass of the dead litter, while in other cases, where all the fœtuses were dead, it appeared as if the fœtuses had died off at different times, for they varied in their degree of development and in their stage of decomposition.

To elucidate the actual cause of fœtal death some does were killed after the injections had been made and before abortion occurred. For this purpose a group of four does was treated in the usual way on the 20th day of pregnancy. One of these was killed on the following day, or 18 hours after the last injection had been given. Reddish brown (decomposed) blood was found in the vagina, obviously having flowed out from the uterine cavity. The amniotic cavities were filled with a bloody fluid, and all the fœtuses had been killed, and were already showing distinct signs of decomposition. The placentas showed a pronounced stage of destruction, and were dark blue in colour, this presumably being caused by acute bleeding into their tissues.

Another doe of this group was killed on the second day after the injections, that is on the 22nd day of pregnancy, and it was observed that some of the fœtuses lying in the ovarian ends of both the uterine

horns were still alive, but that the majority of the young had been killed and were in an advanced degree of autolysis.

The third doe, killed three days after the experiment, on the 23rd day of pregnancy, presented a similar picture of destruction and atrophy inside the uterine horns, but still further advanced than in the former cases.

The last doe, killed four days after the pituitary treatment, on the 24th day of pregnancy, had already aborted and showed only the usual symptoms of recent pregnancy.

These experiments were repeated and gave exactly the same results as before. There again it was found that in one case, which was treated with pituitary on its 21st day of pregnancy and killed three days subsequently, both fœtuses occupying the ovarian ends of the two uterine horns had survived, whilst all the others had been killed.

Although these experiments had given evidence of fœtal death following pituitary action, they had yielded no clear indication of when death actually occurs, nor of what might be regarded as the primary cause of death. In pursuit of this question another group of four does was selected and treated in the usual way on their 21st day of pregnancy.

Two (*a* and *b*) of these were destroyed one hour and a half after the last injection of pituitary had been given. It was surprising to find in one of them (*a*) that the fœtuses were still alive, although apparently injured, as they showed a distinct lack of activity. The placentas, however, looked slightly congested and were a shade darker in colour than usual.

In the second case (*b*), the fœtuses and placentas showed a degree of destruction distinctly more pronounced than in the other doe; the fœtuses were dead, and the placentas congested. In both these cases, however, no free blood could be observed, either in the vagina or anywhere in the uterus.

The third doe (*c*) of this group was killed 5 hours after the last injection had been administered. In this case the effect of pituitary action was obviously more marked than in the other two does. The advanced atrophy of most of the fœtuses showed that they must have died some hours previously. Only the two lying at the ovarian ends of the uterine horns had escaped death up to this time, but they were distinctly inactive.

In the fourth animal (*d*) of this group, which was killed 10 hours after the last pituitary administration, the degeneration of the fœtuses and placentas was more advanced than in the other three.

These experiments showed that the immediate effect of pituitary action on rabbits in the 20th or 21st day of pregnancy was small, presumably causing some disturbance in the fœtal circulation, followed by a slow dying of the fœtuses. It then became of interest to determine whether the same effect was produced by an equal quantity of pituitary extract given to animals in a more advanced stage of pregnancy. For this reason three rabbits were taken, one on the 24th day, the second on the 26th day, and the third on the 28th day of pregnancy; all three were treated exactly in the same way, and were killed 3 hours after the last injection had been administered.

An examination of the organs in these three rabbits showed an astounding amount of destruction increasing with the advance in the stage of pregnancy. In the case on the 24th day of pregnancy the fœtuses were dead and the placenta congested, the degree of disturbance was greater in the second rabbit, and in the third the fœtuses already showed an advanced stage of autolysis; the placentas were black and blood had flowed into the liquor amnii and into the vagina, indicating that the action following the first few injections had been strong enough to kill the fœtuses.

The actual cause of the death of the fœtuses in the experiments of this group was found to be a flow of blood into the tissue of the spongy layer of the placenta. The degree of acute bleeding as an immediate result of pituitary action varied according to the stage of pregnancy at which the animal happened to be. In the earlier stages of pregnancy, as on the 20th day, the effect on the placenta could scarcely be detected by the naked eye when the doe was killed a few hours after the last pituitary injection had been given, though histological preparations showed that some tiny amount of bleeding had occurred as a result of the abnormal tearing of the uterine muscle at the joint layer of the placenta. But as soon as bleeding, however minute in quantity, took place, there was sufficient cause to make bleeding continue indefinitely until large blood-clots were formed, which worked like wedges between the uterine wall and the placenta and finally led to the complete detachment of these two organs. The further pregnancy had advanced the greater was the immediate effect of pituitary action, represented by coagulated blood of increasing amount lying in the meshes of the destroyed tissue of the spongy layer.

Attention may be drawn to the fact that in a number of cases the fœtuses at the vaginal end of the uterine cavity had been killed, whilst those at the top were still alive, as though the pituitary extract had

acted differently upon each part of the uterus. The explanation of this, however, might be that the bottom fœtus has to stand the pressure from all the others lying further up, whilst the one at the top has to bear only the contractions of the surrounding uterine wall. Besides, it may be due also to the way in which the uterus is fixed in position, for the vaginal part of it is certainly more firmly attached to its surroundings than the ovarian part, and thus, the uterus contracting into a fixed point at the bottom, the effects of labour are concentrated at this particular spot. To sum up, it may be said that the effect of pituitary action upon the pregnant uterus during this period consists of some destruction of the tissue of the spongy layer, and that this increases considerably with the advance of pregnancy and causes a corresponding amount of bleeding, which finally brings about fœtal death and abortion.

Group 3. *Covering the time from the* 17*th to the* 1*st day of pregnancy.*

This group of experiments is characterised by the fact that whatever reasonable quantity of pituitary extract was injected into a rabbit in this period of pregnancy it was never possible to disturb pregnancy. The amount of pituitary used at each injection was up to 0·5 c.c. of pituitrin (Parke, Davis), which is equal to 15 mgrm. of moist gland, or 4–5 mgrm. per kilo rabbit. Considering that the average weight of the posterior lobe of the hypophysis in the rabbit is 7·5 mgrm., the quantity of pituitary used for each injection was far in excess of any amount which could possibly be secreted naturally, and therefore was thought to be strong enough to produce a maximum action on the uterine muscle. That the action of such a dose of pituitary was really powerful could easily be observed by the distinct straining which the rabbit showed immediately after the injection, and the frequency of micturition and defæcation gave evidence of its violent action upon the plain muscle of other systems. Twenty-seven experiments were carried out on rabbits which were in the different days of this period of pregnancy, and it was found that no pituitary action could be produced sufficient to disturb pregnancy during this time nor sufficient even to reduce the size of the litters born.

Discussion.

The results obtained in this investigation indicate that considerable changes occur in the relationship between the hypophysis and the uterine muscle during pregnancy, and it is now a matter of interpreting these changes rightly. They may be due to variations in the functions of

one of these organs or in both of them: to decide this question it would appear best to start first with the study of the results in Group 1.

It has been shown that it is possible to induce parturition on any day of this period by stimulating the uterine muscle with a certain quantity of pituitary. But in order to obtain always the same result it is necessary to increase the dose of pituitary from a quantity equal to 0·0075 mgrm. of moist gland on the 32nd and 31st day of pregnancy to one equal to 0·3 mgrm. on the 30th day, and to one equal to 0·6 mgrm. on the 29th day of pregnancy. This looks as though the conditions in the uterine muscle were more or less the same all the time, and as though there were naturally a rapid rise of pituitary secretion finally resulting in labour. As the average weight of the posterior lobe of the pituitary gland in the rabbit is 7·5 mgrm., it seems quite likely that this gland is able to secrete 1/1000 of its total weight per hour, which amount is required to cause birth on the 32nd and 31st day of pregnancy. This sounds acceptable enough; but that there should be an increase of secretion at a rate of 1 : 100, roughly speaking, within two days, is not so easy to believe.

This figure is arrived at as follows. It may be assumed that the uterine muscle does not change in its functions from the 29th day up to the 31st or 32nd day of pregnancy, because it is capable of delivering the young at any time during this period, provided it gets the requisite stimulus from the pituitary. Furthermore, let us suppose that a negligible quantity of pituitary is secreted on the 29th day of pregnancy, and that a dose of pituitary equal to 0·6 mgrm. of moist gland is therefore needed to induce parturition. As roughly 1/100 of that amount only is required to yield the same effect on the 31st or 32nd day of pregnancy, we could say that the other 99/100 of that amount is naturally secreted on these two days, thus stimulating the uterine muscle to such an extent that we have only to add the minute quantity of 0·0075 mgrm. to make the uterus reach the point where it gets rid of its contents. This would mean, in other words, that the pituitary gland would secrete an amount equal to the difference between 0·6 and 0·0075 mgrm. of moist gland per hour on the 31st and 32nd day, or an amount approximately equal to its own weight per day. This would be a considerable but not an impossible quantity. From this argument the conclusion might be drawn that labour is brought about by a sudden increase of pituitary secretion during the last days of pregnancy. If this be a true conclusion, we ought to be able to obtain some confirmation of its truth by studying the results of the second group of experiments.

Coming now to Group 2 of the experiments, we find, however, that

there is a sudden break in the course of events occurring between the 29th day and the 28th day of pregnancy. We find that when the dose is confined within reasonable limits, pituitary injected into a rabbit on the 28th day of pregnancy will never directly cause abortion. The fact that pregnancy can be interrupted by injecting pituitary on the 29th day, and cannot be interrupted by doing so on the 28th day, in spite of using a quantity of pituitary far larger than could ever possibly be secreted by the hypophysis of the rabbit, proves that there must be something besides the pituitary secretion that changes in its function during pregnancy, and this can only be the uterine muscle. The conclusion is that the abortion caused by the administration of pituitary on the 29th day of pregnancy cannot possibly be due to an increase of pituitary secretion in the rabbit, but must depend on some notable change in the uterine muscle occurring at that particular time.

Furthermore, let us consider the immediate effect of pituitary action upon uteri in different stages of pregnancy within this period. Let us suppose that during the time from the 18th to the 28th day of pregnancy the pituitary secretion is more or less steady, as Dixon and Marshall have shown, then one would expect to obtain more or less the same result on any day of this period if an equal quantity of pituitary is always used; but this is not so. It is beyond all doubt that the effect gradually increases when the experiments are carried out in the way described, and that these show only a minute effect at the beginning of the period but end, however, in vast destruction on the 28th day of pregnancy. This is a further proof that the uterine muscle undergoes a remarkable change, at least from the 18th day up to the 29th day of pregnancy.

Lastly, when we follow the results described in Group 3 of the experiments we experience yet another surprise, for we find that the pituitary loses all its power to disturb pregnancy during the first 17 days of gestation. Here again, the remarkable break occurring from the 17th day to the 18th day of pregnancy can be explained only by some cause affecting the uterine muscle. We may be quite certain that we shall obtain maximum contractions of the uterus, lasting at least an hour, when 0·5 c.c. of pituitrin (Parke, Davis) is given to a rabbit. In spite, however, of extending this maximum action over 9 hours, it never results in disturbing pregnancy on any day of this period. Moreover, it does not produce even the slightest influence on the transport of the ova during the earlier days of pregnancy. In view of all these facts, therefore, we concluded that a great change takes place in the uterine muscle, beginning at least on the 17th day and gradually developing

up to the 29th day of pregnancy. This period, in which the change in the uterine muscle is experimentally proved, covers 13 days of pregnancy, but it remains an open question whether the change commences earlier than we are able to recognise it and continues to develop during the last few days of pregnancy or not. In order to solve this question we may consider the evidence supplied by other investigations on the uterine muscle during pregnancy.

It is universally recognised that the increase in weight of the uterus during pregnancy is chiefly due to the hypertrophy of the muscle. Luschka and Veit(3) found in the human uterus that the formation of new muscle fibres is limited to the first three or four months and that from this time onwards only hypertrophy of the existing muscle cells takes place, each cell increasing 7–11 times in length and 2–7 times in width. A similar increase in the size of the uterine muscle during pregnancy may be postulated also of most mammals.

In Fig. 1 is shown a chart kindly given to me by Mr J. Hammond,

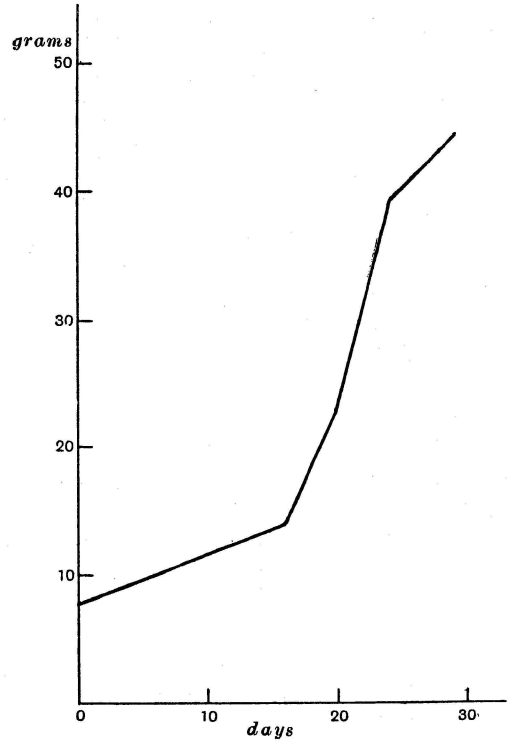

Fig. 1. The rate of growth of the uterine muscle of the rabbit during pregnancy.

which shows the rate of growth of the rabbit's uterus during pregnancy. It gives a clear idea of the slight increase in weight during the first 16 days of pregnancy, and of the rapid growth of the uterus that takes place from this time onwards.

We know very little about the physiology of the uterine muscle during pregnancy, but clinical observations throw some light upon the remarkable change which occurs during its progress. We may quote a statement on this matter from Williams' *Obstetrics* (4): "The increasing readiness with which the uterus reacts to stimulation during the latter months of pregnancy affords abundant evidence of its growing irritability. The intermittent contractions, which occur at intervals throughout pregnancy, come more and more frequently at this time, and occasionally with such intensity that it may be difficult in the last few weeks before delivery to distinguish between them and actual labour pains." This is the point of view expressed in most of the text-books on obstetrics, and adopted in physiology.

Conclusions.

My own interpretation of these facts is as follows. There is no increase of irritability or sensitivity of the uterus during pregnancy, but, corresponding to the growth of each muscle cell, there is a regular rise of contractility of the muscle. The larger the muscle cell the greater is its ability to shorten itself. It is in consequence of this fact that the effect of pituitary extract upon the muscle increases steadily the further pregnancy is advanced. During the first ten days of pregnancy the maximum contraction in each muscle fibre cannot produce a sufficiently great mechanical effect to influence the transport of ova, or to disturb the connection between the uterine wall and the placenta during the subsequent seven days. In other words, at this time the uterine muscle cell has not yet grown enough, as may be seen from the chart (Fig. 1), and so has not yet the power to break down the tissues of the spongy layer of the placenta when it is stimulated by pituitary. The maximum shortening of the cells caused by pituitary on the 18th day, however, has just reached the threshold where the attachment of the placenta begins to suffer, and from this time onwards there is a perceptible increase of effect with every day, the maximum contractions of the muscle following the pituitary administration causing vast destruction between fœtal placenta and uterine wall. The transition of the pituitary effect from the 28th to the 29th day of pregnancy is by no means abrupt, as it might appear; on the contrary, when we look at the enormous devastation effected by pituitary action on the former day we wonder why actual delivery has not taken place. On the 29th day of pregnancy the uterine muscle cells have grown so large that their maximum contraction, caused by pituitary, results in the delivery of young, while in the last few days of pregnancy the uterus keeps on growing and increasing its contractility so that eventually a maximum contraction is no longer needed to produce the young. It has been shown above that there is a difference in the effect following a minimum dose of pituitary and that following a maximum dose given, for example, on the last day of pregnancy. The minimum dose of pituitary at this time may cause the birth of one young, but a larger dose is immediately followed by the birth of the whole litter. By the end of pregnancy, however, the muscle fibres have become enlarged to such an extent and have thus acquired so great a power of contractility that their spontaneous contractions alone finally cause birth. There is no need to postulate any sudden influence or stimulus acting on the uterus at this time, as the labour pains are not essentially different in character from the contractions immediately preceding them, but only slightly more severe in degree, and so are to be regarded as the last step in the series of gradually expanding events.

There are other factors which have been regarded as of importance in the onset of labour and therefore need some consideration. For example, it is said that the loosening of the placenta is indispensable to the delivery of the fœtus. That this is not so can easily be proved. Under normal conditions young rabbits are cast wrapped in the fœtal membranes, that is, the ovum is cast as a whole; but it has been shown above that the young can be cast without their membranes and placentas when pituitary is used, particularly so on the 29th and 30th day of pregnancy. This proves that the actual process of birth is merely a matter of the uterine muscle. In man and many mammals the fœtus is born first and the placenta follows some time subsequently. Furthermore, it is well known that the placenta may not get loose at all, whilst the delivery of the fœtus takes place quite normally. The conclusion to be drawn is, however, that the actual mechanism loosening the placenta as pregnancy advances is due, apart from any retrogressive processes in the placenta itself, to the increasing contractility of the uterine muscle. The placenta is a non-contractile body attached to the uterine wall, which, on the other hand, is continually contracting and extending. So long as the variation in the surface of the uterine muscle is comparatively small, a fixed attachment between these two organs is likely to exist. This is shown in the rabbit by the fact that up to about the 20th

day of pregnancy the placenta can only be separated from the uterine wall by cutting through the close connection between them. As pregnancy proceeds, however, this connection becomes looser and looser every day, so that at the end of gestation the placenta may be squeezed off from the uterine wall with the greatest ease and this loosening would certainly be brought about by the increased activity of the uterine muscle.

It has also been suggested that the size of the fœtus and the simultaneous extension of the uterine wall must be looked upon as important factors in starting parturition. But attention must be called to the fact that in man the duration of pregnancy remains constant in spite of great variations in the size and weight of the fœtus, and in spite of the enormous extension the uterus has to undergo in case of twins or hydramnios. Further, in cases of extra-uterine fœtation, where the fœtus has had a chance of growing up to the normal end of pregnancy, patients feel exactly the same pains at the onset of labour as under normal conditions, and if the placenta happens to be attached to the outside of the uterus it becomes loose in the same way as under ordinary conditions.

In this connection an interesting paper of Sauerbruch and Heyde(5) may be referred to. Using the method of parabiosis they tried to detect whether birth occurring in one of two partners influences the pregnancy of the other. Five experiments were carried out on rats, each rat of a pair being at a different stage of pregnancy. In two experiments the animals lived together for a week when one in each pair bore a normal litter without affecting their partners, which cast their young a fortnight later at their normal end of pregnancy. In the other three experiments the rats lived together longer, and the difference in the stage of pregnancy was not so great. Yet, in spite of the difference in the stage of pregnancy, labour started almost simultaneously in both animals and resulted in a litter of normal young in one, and an abortion of underdeveloped fœtuses in the other partner. The authors conclude that the lack of mutual influence between the two partners observed in the former experiments was due to want of sensitivity of the uterine muscle in the partners that were at the beginning of pregnancy.

In another investigation on the induction of labour by injections of fœtal serum Heyde(6) again comments on the lack of sensitiveness of the uterus at the earlier stages of pregnancy.

When we consider further how much effort has been expended, both legally as well as illegally, in attempting to discover a drug that will excite the uterus sufficiently to induce abortion, and how all this effort has been in vain, we may say again that this failure is due to lack of sensitivity of the uterine muscle at the time.

Lastly, we have to consider on what the growth of the uterine muscle during pregnancy depends. It can be at any rate stated that its growth is due to a hormone influence and not to anything else. So far as our present knowledge goes, we are entitled to regard the presence of the corpus luteum as the main factor in causing the growth of the uterine muscle, and this is particularly clearly illustrated in pseudo-pregnancy.

Hammond(8) has shown that in the rabbit the removal of the ovaries at any time during pregnancy is followed either by absorption of the fœtuses or by abortion, this being almost certainly due to the disappearance of the corpora lutea. The reason why pregnancy ceases to go on under these circumstances is that the uterus immediately shrinks and atrophies. These facts and the results obtained in the present investigation furnish ample evidence that abortion occurring at earlier stages of pregnancy cannot be regarded as the effect of any activity of the uterine muscle, but rather as the consequence of some disturbance in the supply of the necessary hormones.

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