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PITUITARY EXTRACT IN OBSTETRICAL PRACTICE

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IT seldom happens that a new drug or remedy comes into universal use in such a short space of time as has been the case with pituitary extract in obstetrical practice. Since it was first used clinically by Blair Bell in 1909 it has been employed in practically every obstetrical clinic throughout this continent, and in Britain and Europe. The result is that in these four years a vast amount of literature has accumulated on the subject. It seemed to me that a useful purpose might be served in reviewing this literature, and in affording an opportunity for discussion amongst those of us who have used the drug, and have not up to the present put our results upon record.

Any new remedy is apt at first to be used somewhat indiscriminately, and this has been the case with pituitary extract. We can, however, learn a great deal from such experiences, for it is only by a consideration of a large number of cases, and by a study of the good and bad results obtained under different circumstances, that we can arrive at a proper conclusion regarding its sphere of action and its limitations.

Anatomy and Physiology. The pituitary body is situated in the sella turcica, at the base of the skull. It consists of two lobes, an anterior and a posterior, connected by the pars intermedia. The posterior lobe is connected with the floor of the third ventricle by

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the infundibulum. In the female the body is about one-tenth heavier than in the male (Biedl: *Innere Sekretion*, Berlin, 1910). The weight is always increased during gestation, and while diminishing again post partum, remains greater in multiparæ than in nulliparæ.

The two lobes differ in size, in structure, and in function. The anterior is the larger of the two. It consists of a stroma of connective tissue, containing epithelial cells arranged in a glandular fashion. These cells are of two types, those which stain deeply with the ordinary stains—some being eosinophile and some basophile—and those which stain feebly. It is to the increase in size and number of these latter cells that the increased weight of the gland during pregnancy is due. At the same time they change in character and in staining reactions. The epithelial cells of the anterior lobe produce a colloid substance. Destruction or removal of this lobe in adult animals results in their death. Young animals may, however, survive the operation, and in them marked effects are produced; they take on fat rapidly and sexual development is arrested, the genital organs remaining in an infantile condition. The same results have been observed to follow disease of the gland in the human subject. The anterior lobe therefore has important influences on the development of the genital system and on the maintenance of its functions.

It is, however, more particularly with the posterior lobe that we are concerned in practical obstetrics, for it is that lobe which contains the substance which has such marked effects in uterine contraction. This lobe has a structure entirely different from that of the anterior. It is developed from the floor of the third ventricle, in distinction from the anterior, which develops from the stomatodæum. It is composed of ependyma, neuroglia cells, and small islets of epithelium. Animals may survive for a long time after its removal. Extracts prepared from it have very pronounced effects on non-striped muscle and on certain of the other tissues of the body.

Action of Pituitary Extract. The function of the pituitary body has been investigated by Herring, by Schaefer and Oliver, Dale, Bell, Otto, Scott, Swale Vincent, and many others. Schaefer and Oliver showed that extracts of the gland produced a marked rise in blood pressure, owing to constriction of the peripheral vessels. They also demonstrated its diuretic action, due partly to a dilatation of the renal vessels, and possibly to a direct action on the kidney cells. The latter observation Merrill failed to con-

firm. Besides its action on the peripheral circulation it has a direct action on the heart, causing strengthening and slowing of the beat. Dale was the first to demonstrate its action on the uterine muscle. Later Fränkl-Hochwart and Fröhlich carried out a series of experiments, showing that pituitary extract caused marked contraction of the uterus of pregnant and lactating animals, and rendered it much more sensitive to Faradic stimulation. These results have been confirmed and amplified by other observers (Bell, Cushny, Falta and Fleming, Klotz, etc.). Fränkl-Hochwart and Fröhlich obtained their results only in pregnant and lactating animals. The results are always most pronounced in the pregnant uterus, but can also be demonstrated in the non-pregnant organ.

The active substance contained in the gland has been investigated by several observers. Führer found that β -imidazoly-lathylamin (histonin) closely resembled pituitary extract pharmacologically, but he does not believe that it represents the influential constituent. Houssay and Ibanez (*Presse Médicale*, May, 1912) have isolated from the posterior lobe a crystalline substance which is diuretic, and which has all the effects on non-striated muscle that the whole extract of the gland possesses. They state that it is much more reliable than the whole extract. Herzberg states that the active hormone has been isolated by Meisher, Lucius and Brüning. It is put up for use as hypophysin sulphate. He has used a 1 in 1,000 solution in thirty-two cases, and finds that it possesses all the advantages of pituitary extract and is free from bad effects.

Blair Bell, in 1909, was the first to apply in practice the results of the experimental investigations carried out up to that time. He used the extract with good results in cases of post partum hæmorrhage, placenta prævia, and to minimise hæmorrhage in Cæsarean section. After him Hofbauer published his results, and since then records have been rapidly accumulating.

When administered to a woman in labour the extract quickly causes an increase in the strength of the uterine contractions, while the duration of contraction becomes prolonged and the intervals between pains shortened. The first contractions may be somewhat tetanic in character (a point which is taken up later), but very soon they resume their ordinary rhythmic character, and apart from their increased force do not differ from normal. When administered during the first and second stages of labour results are practically constant. These results are always most apparent if the pains have been previously feeble, and occurring only at long intervals.

On the normal contractions little effect may be produced. As regards its action in the early months of pregnancy in the induction of labour and post partum, clinical records are at variance, and to a consideration of these attention will be directed later.

Mode of Administration. Most of the extracts now on the market are prepared from the posterior lobe, a few from the whole gland. It is, however, from the posterior lobe that the active substance is obtained. Pituitrin, pituiatrin, pituglandol, glandiutrine, hypophysin sulphate, vaporal, are some of the names under which it is sold. There seems to be little or no difference in the activity of the preparations put up by different firms. The preparations I have used have been those prepared by Messrs. Duncan, Flockhart & Company, Edinburgh, and Burroughs Wellcome & Company. Sterilization by heat does not destroy its action, and it is usually put up so sterilized in glass ampules, and is ready for hypodermic, intramuscular or intravenous injection. When administered by the mouth, even in large doses, little or no effect is produced upon blood pressure or uterine contraction (Foges & Hofstaetter). The most convenient way to give it is by subcutaneous or intramuscular injection. The latter is the method I prefer, as it seems to me to act more quickly and powerfully than when given subcutaneously. I cannot help feeling that some of the comparative or complete failures recorded have been due to the subcutaneous method of administration. No pain follows the injection. Hofbauer has used it intravenously, and finds it acts very quickly and powerfully on the uterus. Certain unpleasant symptoms, however, such as pallor, cyanosis, perspiration and a sense of oppression, sometimes resulted, and in ordinary cases this method cannot be recommended. Where very prompt action is required, as in cases of post-partum hæmorrhage, it might with advantage be employed. Hofbauer warns against leaving any trace of alcohol in the syringe used for administration of the drug, stating that it interferes with its action, but this observation has not been confirmed by subsequent observers. I have taken no such precautions, and have seen no bad results.

Dosage. The dosage is fixed in terms of gland weight. Recently Dale and Laidlaw (*Journ. Pharmacol. & Experimental Therap.*, September, 1912) outlined a method for the standardizing of extracts by using the isolated uterus of the virgin guinea-pig, which gives uniform resistance to successive equivalent doses. One cubic centimetre of the extract, which usually represents 0.2 grammes of gland substance, is generally regarded as the full dose. I have employed as a routine a dose of 10 min. There is

no cumulative action of the drug, and large quantities may be given without bad results. Hofbauer has given 7 cc. within twenty-four hours. Bab, in treating cases of osteomalacia, has given 2 cc. in a single dose daily over a period of a month without any bad effect. One of his cases had as much as half a litre altogether.

In animals large doses often result in glycosuria, but this is as a rule only temporary (Miller and Lewis, *Johns Hopkins Hospital Bulletin*, February, 1913). It has been found experimentally in animals that a second dose administered shortly after the first has very little effect in further raising blood pressure, while succeeding doses fail to produce any effect at all.

When given to the patient in labour a single dose produces a marked effect on uterine contractions, usually within ten minutes of administration, and the maximum result is obtained in from half an hour to an hour and a half after. Thereafter the effects gradually pass off, but, in contrast to the results obtained experimentally, a second injection again stimulates powerful contractions. If a single dose has had little or no effect after the lapse of ten minutes, a second injection may produce results.

We shall now take up in detail the different indications for use in obstetrics.

To accelerate labour when already in progress. We take up this aspect of the subject first because the action of pituitary extract is most certain and attended with the fewest side effects when given after labour has been in progress for some time, and pains have become feeble and infrequent. Hundreds of such cases have now been recorded, and it would serve no useful purpose to recapitulate them. Nor do I intend to give details of all my own individual cases. I shall content myself with giving the general conclusions arrived at from the study of all these cases, and refer shortly to one or two of special interest, which I have myself observed.

The results are more certain in the second stage than in the first, and the lower the head is in the pelvis the more pronounced the effect of the drug. If the head has been down in the pelvis for some time, and remains there owing to feebleness of the pains, a single injection of 1 cc. or less usually results in its expulsion within half an hour, and very often in a much shorter space of time. Bondy, for instance, found that patients in whom the average duration of labour had been thirty-six hours were spontaneously delivered within an average space of twenty-eight minutes after the pituitary injection. We have frequently observed delivery take

place in such circumstances as the result of a single strong pain within five minutes of the administration of the drug. The drug is equally efficacious whether the inertia be primary or secondary. Its timely use in such cases will save many a forceps operation. This is a point emphasized by Voigt. Hamm states that since using pituitary extract forceps were required only twice in three hundred deliveries. In the Strasburg clinic, where his observations were made, forceps were used formerly in 3.9 per cent. of cases. Typical examples may be given, similar to many others in the literature.

Mrs. R., primipara; confined in the Toronto General Hospital, December 6th, 1912. Pelvic measurements normal. The first stage of labour was prolonged, and at the end of twenty-four hours pains were feeble and dilatation incomplete. So morphia (a quarter of a grain) was given. She rested for eight hours, and then pains began again, and in an hour the os was dilated and membranes ruptured. The head was well down in the pelvis, but the pains became more and more feeble, and at the end of four hours no progress had been made. Ten minims of pituitary extract were given. Strong pains began within three minutes, and in five minutes more the head was born. The rest of the labour was perfectly natural. The placenta was spontaneously expelled half an hour after the birth of the child. Blood loss slight; uterus remained strongly contracted.

Equally good results are recorded in cases of delay in the second stage, due to causes other than mere feebleness of uterine contractions, such as size or malposition of the head, face and breech presentation, twin pregnancy, and minor degrees of contraction of the pelvis, conditions which, without the use of pituitrin, would often have called for operative interference.

Persistent Right Occipital Position. Mary R., multipara; confined in Toronto General Hospital at full term on April 12th, 1913. Pelvic measurements normal. R.O.P. position. Admitted in labour with os fully dilated and head down in pelvis. Had been in labour twenty-one hours. After admission pains were feeble. The head remained in the perineum for two hours. Ten minims pituitary extract were given. Strong pains came on in seven minutes, and in half an hour the head was born face to pubes. Perineal laceration of first degree. Rest of labour normal.

Twin Pregnancy. Mrs. M., multipara; confined in Toronto General Hospital at eight and a half months on April 19th, 1913. Patient was admitted in labour. It was noted that the abdominal tumour was large, but the diagnosis of twins was not made. Pains

were feeble and ineffectual from the beginning. The os was fully dilated, and the membranes ruptured after thirteen hours. Head quickly came down in perineum, but then pains got feeble, and no progress had been made at the end of two hours. Ten minims pituitary extract were given. Pains became stronger within five minutes, and occurred more frequently. First child born ten minutes later, followed in two minutes by second child, and in twenty minutes by the placenta. Uterus contracted strongly after, and there was practically no loss of blood.

In patients with *slight contraction of the pelvis* the use of pituitary extract may save a forceps extraction. Hamm records two cases, in which spontaneous delivery occurred after a single injection, and in which, owing to a slight contraction of the pelvis, forceps extraction had failed before the patients were admitted to the hospital. Even if forceps should ultimately be required in a narrow pelvis, the more powerful contractions induced help the moulding of the head and render extraction easier. If the drug is going to act it will do so within ten minutes, and so no time is lost. There are many cases on record where an injection was given, and forceps were being prepared, but delivery has taken place before the instrument could be sterilized.

In such minor degrees of pelvic contraction Hengge and Grünbaum have had good results. Vogt states that in six hundred cases in the Dresden clinic, among which were a number with narrow pelvises, forceps were never used. Fries states that a number of times he has seen the entrance of the head into a slightly narrow brim helped by the use of pituitary extract. The contraction must of course be of such a degree as to allow of the passage of the head. The drug has no place in the treatment of labour in a markedly contracted pelvis.

Linzenmeier enters a plea for its use after the operation of pubiotomy. He deplors the discredit into which the operation has fallen, owing chiefly to the tearing of the soft parts and subsequent sepsis, due to instrumental delivery after section of the bone, and records two cases in which he used pituitary extract with happy results. In one the membranes ruptured early, and a hydrostatic dilator was inserted into the cervix and 1 cc. of pituitary extract given. After full dilatation the head failed to engage in spite of the Walcher position. Left-sided pubiotomy was performed and another cc. of pituitary extract given. The child was born spontaneously in thirty-five minutes without any tearing of the soft parts. In another case the child was born as the result of four

uterine contractions induced by 1 cc. of the extract, given immediately after section of the bone.

When given late in the first stage of labour the results are almost equally as good as in the second stage. If the os is almost completely dilated, and progress arrested owing to feebleness of the pains, a single injection is usually sufficient to effect full dilatation. In such cases the drug is of the greatest service. Under such circumstances the practitioner is tempted to terminate the case by the application of forceps, a mode of interference which is too often attended with extensive cervical lacerations. Pituitary extract does all that is needful, and thus saves the patient from operative interference and from possible ill health afterwards, resulting from extensive tears.

In the earlier part of the first stage the results are not quite so certain, but they are better in multiparæ than in primiparæ. In the latter, if dilatation has only just begun, spasm of the internal os may result and labour be retarded. We shall refer more fully to this when speaking of the bad effects of the drug.

In post-partum hæmorrhage. It was in the treatment of post-partum hæmorrhage that pituitary extract was first used by Blair-Bell, and later by Foges and Hofstätter. They found it efficient, even in severe cases. Good results have also been reported by Aarons, Eisenbach, Schmidt, Gussew, Herzberg and others. There is, however, a considerable diversity of opinion as to its efficacy in these cases, the majority agreeing that it is less efficient than some of the ergot preparations. Hofbauer, for instance, found that the results are very uncertain. The mode of administration may have something to do with its failure in the hands of some of these writers. Most of them employed the subcutaneous method, and as we have seen the action of the drug is slower when given thus than when given intramuscularly.

Klotz has treated eighteen cases by the intramuscular method with good results. In two of these ergotin had no effect, but powerful contractions resulted in less than three minutes after the pituitary injection. Schmidt got good results in a case where a subcutaneous injection failed by injecting directly into the uterine muscle through the abdominal wall. In a case of Cæsarean section he induced powerful contractions in a similar way by direct injection. In another case he got a good result by injecting the drug into the uterine wall with a long needle passed through the cervical canal. Gussew by its use was able to control severe post-partum hæmorrhage after vaginal Cæsarean section.

A previous injection of pituitrin has the effect of sensitising the uterus, and rendering the action of the ergot preparations more certain (Herzberg). Kroemer has in this way found that it acts well with secacornin.

Personally, I have had no opportunity of using it in a severe case of post-partum hæmorrhage. In hæmorrhages of a minor degree, due to slight atony of the uterus, I have always found intramuscular injection to be followed by powerful contraction, with cessation of the bleeding.

In Induction of Labour. After the effect of pituitary extract on uterine contractions had been demonstrated it was not long before it was tried for the induction of labour, and a considerable number of observations are now on record. The results obtained, however, have not been altogether satisfactory. In the early months of pregnancy its effect is very uncertain, but towards full term better results may be obtained, and at term and in post-mature cases a good effect is till more to be depended upon. When given for the induction of abortion in the early months the results are almost invariably negative. Sometimes it has no effect whatever in producing uterine contractions; in other cases contractions are induced, but they have little effect in opening up the cervix and quickly pass off. In others it retards progress by causing a spasm of the os. For the treatment of incomplete abortion also it is not to be recommended. Hale has used it in twenty-seven cases, giving daily subcutaneous injections of 2 cc. of the extract. Pains were induced in almost all the cases, and in some were quite severe, but twenty-two out of the twenty-seven were failures, and the ovum had subsequently to be removed manually.

Neu reports the case of a woman three months pregnant, whom he treated for osteomalacia with large doses of pituitrin without producing any effect on the pregnancy. Schaefer failed to induce abortion at the third and at the fifth month, even by giving 3 cc. in the course of twenty hours. In a case at the sixth month, after pains had been in progress for some time, two injections resulted in spontaneous expulsion of the ovum. Hamm reports a case in which he gave 1 cc. in order to terminate pregnancy at the fourth month. The cervix was at the same time plugged with gauze. Two further injections were given at intervals of two hours. When the tampon was removed the internal os was found to be firmly contracted in a spasmodic fashion, and only relaxed when the patient was deeply anæsthetized. In another case he tried to induce abortion at the third month in a patient with tuberculosis. She had three injec-

tions daily for three days with no result. A tent was then inserted, and another three injections given. Uterine contractions were strong, and the tent was expelled. The internal os, however, was found to be in a stage of spasm, and the uterus in tonic contraction. The ovum was removed only with the patient in deep narcosis, and after multiple incision of the cervix. In another case at the six month the cervix was plugged and five doses of pituitrin given. Pains resulted, but he found, on removal of the plug, that the internal os contracted spasmodically during the pains, admitting then one finger only, whereas between the pains it admitted two. Under anaesthesia this spasm relaxed, and the uterus was easily emptied.

Rieck gave pituitary extract in the hope that the placenta, retained after the expulsion of a four months foetus, might be expelled spontaneously. Strong pains resulted, but the internal os became closed, so that it was impossible to introduce the finger. The next day it was soft and easily dilated. Eisenbach reports two failures, one a missed abortion at the third month, and the other at the fifth month. Hirsch, in five cases, states that in one only did complete expulsion of the ovum occur without further treatment.

I have myself tried it in two cases of incomplete abortion, with retention of the placenta, between the third and the fourth month. In neither of them did spontaneous expulsion occur. Each had two injections within two hours of each other, but no pains were induced, and no spasm of the internal os was observed.

It will thus be seen that in the early months, whilst uterine contractions may be induced, these are usually insufficient to expel the ovum, and its expulsion is further impeded by spasmodic contraction of the internal os. It should therefore only be given in cases where the os is widely dilated. In septic cases, with retention of the ovum or part of the ovum, it should not be employed, as the stricture of the os may render manual separation more difficult than it would otherwise be.

In the induction of premature labour the results are somewhat better, although by no means uniformly satisfactory. Stern was among the first to employ it for induction, and he succeeded in two cases out of three. In both the indication was tuberculosis of the lungs and larynx, and in each spontaneous delivery occurred. I have used it successfully in a similar case.

Mrs. A., aged thirty-five, primipara. Suffered from phthisis for several years. Was seen in consultation when at the eighth month of pregnancy, when the patient was much exhausted, suffer-

ing from night sweats, sleeplessness and general weakness. Termination of the pregnancy was clearly indicated. At 2 p.m. 10 minims pituitary extract were given intramuscularly. Within ten minutes a powerful contraction of the uterus occurred, tetanic in character, and lasting nearly four minutes. This was followed by regular rhythmical contractions. At the end of three and a half hours pains began to pass off, and a second similar dose was given. Thereafter the pains continued regularly, and the child was born spontaneously at twelve midnight. The cervix dilated somewhat slowly, and the doctor in attendance assisted dilatation with the fingers. The child, when born, was asphyxiated, but revived. It died suddenly three days later; cause unknown. The mother also died on the eighth day of the puerperium, the cause of death being pulmonary tuberculosis.

Herzberg reports a successful case of induction one week before term, the indication being the presence of a large umbilical hernia. Two injections of 1 cc. each were sufficient, spontaneous delivery occurring twenty-five hours after the first. In three primiparæ, three weeks short of term, he succeeded in inducing regular labour pains as the result of two injections, but the labour did not progress.

Fries was successful in inducing labour at the thirty-sixth and the thirty-eighth week in two patients suffering from nephritis. Goebel induced labour at the eighth month in a parous patient with a flat pelvis. The first two children had been perforated, and the third delivered by pubiotomy. A hypodermic injection of pituitrin started labour, and spontaneous delivery occurred eleven hours later, the child weighing 3,600 grammes. Hofbauer reports one successful and one non-successful case.

These successful cases are the exception, and a great number of unsuccessful results are recorded. Vogt failed in four out of seven cases. Nagy, Zinnssen, Hamm, Hirsch and Schaefer report cases where it failed. In many of these labour was ultimately brought on by means of the bougie or hydrostatic dilator. In some of them difficulty arose from spasm of the os.

At full term and in post-mature cases the results are more certain. Fries was successful in two normal cases at full term. Herzberg also succeeded with two patients, one of them an epileptic, labour lasting ten hours in one case and eight and a half hours in the other. Krakauer brought on labour in an eclamptic at full term.

I can report one such case. Mary T., aged nineteen; last menstruation May 14th, 1912; estimated date of labour, February

21st, 1913; course of pregnancy normal. Pelvic measurements: interspinous, 27 cm.; intercrystal, 28.5 cm.; external conjugate, 17 cm.; true conjugate, 9.75 cm. Vertex presentation; R.O.P. position. Head not engaged in brim. As the pelvis was narrow it was thought undesirable to allow the patient to go beyond full term. On February 22nd she was given 10 minims of pituitary extract intramuscularly at 5.30 p.m. Pains came on within fifteen minutes, and lasted for about two hours. A second dose was given three hours after the first, and the pains again became strong, but passed off at the end of four hours. At 12.30 p.m. the next day she had another 10 minims. Pains again strong, becoming feeble after two hours, when another injection was administered. Thereafter the labour went on normally, and the child was born spontaneously at 12.55 a.m. on February 24th, after long rotation of the head.

Stolper was successful in inducing labour in two post-mature cases, one twenty and the other fourteen days over term. In both the cervix was shortened, and admitted a finger with difficulty, but there were no pains. One required three and the other four doses, and in both spontaneous delivery occurred. Both had had prolonged labours previously, but as the result of the pituitrin the one terminated in five hours and the other in six. Hagen had a similar result in a multipara fourteen days after term. Two doses were required; the child was born spontaneously eight hours after the first.

I can report a successful result in a similar case:

Mrs. M., primipara, aged twenty-one; last menstruation July 29th, 1912; estimated date of labour, May 5th, 1913; pelvic measurements normal; head presenting; R.O.P. position. On May 27th there was no indication of labour beginning, and the head was not engaged in the brim. At 2.20 p.m. 10 minims pituitary extract was given intramuscularly. Labour pains began after fifteen minutes, and continued strongly until 5 p.m., when they became feeble. At 6 p.m. 10 minims given intramuscularly. Pains again became strong; os was fully dilated at 11.30 p.m.; head came down on to the perineum at twelve midnight, and spontaneous delivery occurred at 1.35 a.m., May 28th.

We were thus successful in inducing labour in three cases in which we used pituitrin, one at the eighth month, one at full term, and one three weeks post-term. Such success is not in accordance with the experience of most other obstetricians, and a number of those who have written on the subject have come to the conclusion that pituitrin ought not to be used at all for the induction of labour.

The results, however, are better at full term and after term than in premature cases, and I am sure that a further trial is justified. The important point to attend to is to administer a second dose before the effects of the first have passed off. If the contractions are sufficiently strong to dilate the cervix the rest of the labour usually goes on naturally. If therefore as a result of one dose only a small amount of dilatation occurs, and no second dose is given, the cervix may again close and labour pains cease. In post-mature cases it can do no harm, and is certainly worth trying before adopting other means.

For the induction of labour in cases of eclampsia its use may be attended with some danger. Blood pressure, already high, may be raised to a dangerous degree. Fries, however, used it successfully in two cases of nephritis, and Krakauer and St. Antechi and Zakczewski used it in cases of eclampsia, both in the first stage of labour. In the latter's case the pulse was slowed from 160 to 76. Several fits occurred after delivery, but another dose of pituitrin was given, and the fits ceased. Bad results are recorded by Nagy, Schneider-Sievers and Tipfer.

Placenta Prævia. A number of very successful results in the treatment of placenta prævia have been recorded. In the absence of pains or when the pains are feeble a single injection very often stimulates strong contractions, so that the presenting part is pressed down against the lower uterine segment and hæmorrhage is arrested. Hofbauer recommends that in lateral and marginal placenta prævia, with the head presenting, the membranes be ruptured and pituitrin injected. If the placenta stretches half way across the os, he inserts a hydrostatic dilator. Trapl adopts the same line of treatment, and in a series of sixteen cases had no maternal mortality, and a foetal mortality of only three, and in two of these the child was dead before the pituitrin was given. Five were marginal, ten lateral and one central. Pituitary treatment may also be combined with version in such cases. The strong contractions pressing down the breech stop hæmorrhage, and there is no need to hurry the labour. In the same way the hydrostatic dilator acts more efficiently when a pituitary injection is given. Gall, in a series of nine cases of central placenta prævia used pituitrin in combination with turning in four, and with hydrostatic dilators in four. The hydrostatic dilator was used where the cervix was not sufficiently dilated to admit the hand. In all cases the bag was expelled within fifty-five minutes of its introduction, and turning was then performed, and a second injection of pituitrin given. In all cases

birth occurred spontaneously within an hour. In six of the cases the foetal heart could be heard before the administration of pituitrin, and in all of these the child was born alive. In none were there any tears of the cervix. Others who record similar good results are Reik, Fischer, Hirsch, Merkel and Blair-Bell. I can report one successful case:

Mrs. C., aged thirty-three; 2-para; was admitted to Toronto General Hospital in December, 1912, the estimated date of labour being January 12th, 1913. Five weeks previous to admission the patient had vaginal hæmorrhage, which lasted for four days; a week later another hæmorrhage, which lasted for two days. Since then, up to the time of admission, there had been intermittent hæmorrhage, lasting for a day at a time. On the morning of December 9th she had severe hæmorrhage, accompanied by slight abdominal pain. When admitted the hæmorrhage had ceased, and the vagina was full of large clots. The cervix just admitted the tips of two fingers, and the margin of the placenta could be felt just within the os. There were no pains present. The vagina was packed tightly with gauze. The patient had no pains during the night, and there was no more hæmorrhage. When the gauze was removed next morning it was found that the cervix had contracted, so that it only admitted one finger with difficulty; no pains were present. The vagina was again packed, and 10 minims of pituitrin given intramuscularly. Fifteen minutes later pains came on, and blood soaked through the packing. Half an hour after the injection the plug was removed, and the cervix was found dilated to the size of a silver dollar. Bipolar version was performed and one leg brought down. Strong contractions continued, and spontaneous delivery occurred within half an hour. A considerable amount of hæmorrhage occurred afterwards, most of which came from a tear on the left side of the cervix. This was stitched, the uterus contracted strongly, and the patient made a good recovery. The eight months child was born alive, and left the hospital with its mother at the end of three weeks.

In this case the pituitrin induced labour pains, and enabled turning to be performed much sooner than would have been the case had it not been employed. It accelerated the course of the labour. Tearing of the cervix may have resulted from very powerful uterine contractions, but we know that such tears are apt to occur through the softened vascular cervix in cases of placenta prævia.

In Cæsarean Section. When given about two minutes before

the performance of the operation of Cæsarean section pituitrin has a marked effect in diminishing the loss of blood. A number of operators, among them Foges and Hofstaetter, Hofbauer, Blair-Bell, Herzberg and Kroemer, have used it for this purpose. In the Tarnier clinic it was found to be inefficient in two cases out of four, and in these ergotin gave good results. Fischer injected it directly into the uterine wall, and the uterus at once contracted and all hæmorrhage ceased. Metzger and others hold that ergotin gives better results.

In other conditions in which pituitrin may be used in obstetrical practice mention may be made of osteomalacia. The influence of pituitrin upon the growth of bone is well known. Extracts have been tried in cases of osteomalacia by Kratochivil, Bab and others. It is stated, however, that while it may relieve the pain, it does not effect a cure.

The extract has also been successfully employed as a galactagogue. I have used it in several cases where there seemed to be a deficiency in the quantity of milk. It was difficult to estimate the exact effect produced, but it was noted in all cases that the children, who formerly appeared to be hungry after feeding, were satisfied and quickly gained in weight.

Action on Bowels and Bladder. In post-partum abdominal distension and retention of urine a dose of pituitrin often sets up peristalsis and stimulates the bladder, so that enemata can be dispensed with and the catheter is no longer required.

Let us now look at some of the bad results which are on record. We shall take up first of all bad effects on the mother.

In some women, more especially elderly primiparæ, the drug appears to have no effect at all. In others it may produce general symptoms, cardiac distress, vertigo, tachycardia, and respiratory difficulty, which have been reported by various writers. The same set of symptoms was observed by Hofbauer after intravenous injection, and it may be that some of those results following subcutaneous or intramuscular injection may have been due to the needle entering a vein.

In its action on the uterus it may set up tonic or tetanic contractions, and may cause a spasm of the internal os. The first contraction after the injection is given is usually a prolonged one. Hamm, for instance, reports a case in which four injections were given. After the second the first pain lasted eight minutes, after the third eleven minutes, and after the fourth seventeen minutes. Schaefer noted in one case that the initial pain lasted for four

minutes. After this first powerful contraction the uterine action is usually normal. Voigts noted these prolonged contractions in three cases. Jaeger and Voigt also noted them. Such prolonged contractions usually result in a marked slowing of the foetal heart, but the child is seldom in real danger, as the ordinary rhythmic contractions succeed the tonic opening one.

Mackenrodt observed tetanic contractions after the use of 1 cc., which resulted in the death of the child before forceps delivery could be effected.

When the contractions are very powerful and painful they may be controlled by the administration of an anæsthetic, or by the use of morphia or omnopon. The ordinary scopolamin-morphine method may be successfully used along with pituitrin (Gisel).

Hertz has seen rupture of the uterus occur as the result of pituitary fluid. The patient was an anæmic primipara, with a ricketty and slightly flattened pelvis. Head presentation; cervix far back in the pelvis. When the os was dilated to admit two fingers the pains ceased. 1 cc. pituitrin given. In three minutes pains began, but in twenty minutes they became tetanic in character, lasting from two to seven minutes. An hour after the injection a very strong tetanic contraction was followed by collapse of the patient. Examination showed that the head had come down into the pelvis. In spite of pantopon excessive contractions continued, and delivery was effected with forceps. It was then found that the anterior part of the cervix had been torn away completely from the vaginal roof, and the descent of the child had taken place through this tear, and not through the cervical canal.

Spasm of the os may occur in cases of abortion, when the drug is given for the induction of premature labour or early in the first stage. We have referred to some of these cases in dealing with the induction of abortion. Heil reports a case where the birth of the second of twins was arrested, owing to spasm of the os following pituitrin injection. Mackenrodt, Patek, Reik and Hamm report this spasmodic contraction of the os after the use of the drug. Nagy had to incise the cervix in one case, owing to spasmodic rigidity. Roemer had to remove the placenta manually in two cases, owing to stricture of the os. White reports a similar case. In a case of sacculated retroflexed uterus, with forward displacement of the cervix, Koch inserted a hydrostatic dilator and gave 1 cc. pituitrin. Strong contractions occurred, but no dilatation of the cervix took place. Apparently there was a spasm of the os. Cæsarean section was ultimately performed, but the child died.

Atony of the uterus post partum. A number of cases have been reported in which pituitrin was given, and in which atony of the uterus occurred after the termination of the third stage. In most of these the last injection had been given a considerable time before the birth of the child. When the last injection has been given within a short time of the birth of the child and placenta, the uterus usually remains firmly contracted. If there is any tendency to relaxation the ergot preparations usually act well, as the uterus appears to be sensitized by the pituitrin.

Bad Effects on the Child. Any bad results on the child are due to the prolonged contraction of the uterus. In nearly all cases marked slowing of the foetal heart is observed, but usually the child is in no danger. Jaeger has noted in one case a fall in rate of 40 per minute. Lieven found in one case that the foetal heart fell to 82, and was very weak. Delivery was effected with forceps. The child was born deeply asphyxiated, and did not recover for a considerable time. Voigt states that he has noted great slowing of the heart, and has never seen meconium passed so freely during birth in other labours as after the use of pituitrin. Nagy had to deliver rapidly with forceps in one case in order to save the child, which was born in an extremely asphyxiated condition. Koch and Spaeth report death of the child in breech presentations after pituitary injections. In both cases delivery was rapid and easy.

Unusual effects have been mentioned in a few cases. There was spasm of the glottis in one case reported by Hamm, and contracture of the extremities, lasting for twenty-four hours, in a case reported by St. Antechi and Zaczewski. It is difficult to say whether these were due to the pituitary or not.

To sum up we may state that:

1. Pituitary extracts have a powerful effect in inducing and in strengthening uterine contractions.
2. The type of contractions induced is similar to that which occurs normally, although at first there may be a tendency to prolongation of the pains.
3. Such prolonged contractions result in slowing of the foetal heart, but the child is seldom in danger.
4. When given in the late part of the first and in the second stage of full time labour the polarity of the uterine contractions is not interfered with, but in early abortions and early in the first stage a simultaneous spasm of the os may occur.
5. Its chief field of usefulness is in the first and second stages of labour, when there is delay due to feebleness of the pains, alone

or when combined with other complications, such as malpositions of head, malpresentations, multiple pregnancy, slight narrowing of the pelvis, etc.

6. In the induction of abortion, in the treatment of abortion already in progress, and in incomplete abortion, its action is so uncertain that it is not to be recommended, except in cases where the os is widely dilated.

7. In the induction of premature labour its effects are uncertain, but if sufficient dosage be given they may be good.

8. In the induction of labour at full term and after better results are obtained than in premature cases.

9. It gives good results in many cases of post-partum hæmorrhage, but is not superior to the various preparations of ergot. It has the power of sensitising the uterus, so as to allow these preparations to act more powerfully, the combination being most effective.

10. It is a useful adjunct in the treatment of placenta prævia, used in conjunction with rupture of the membranes, the use of hydrostatic dilators, or turning.

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