close quantitative agreement with those obtained with sodium chloride. The assay of such response to sodium chloride is illustrated in Fig. 5. The response to the intracarotid infusion (black circles) lies for most of its course between the responses to 0.67 (black-and-white circles) and 1.17 (open circles) μU/sec., being nearer to and probably a little less than the latter: it is assayed as having a post-pituitary-extract equivalence of 1 μU/sec.

Conclusions from Results of Long-period Infusions

Three conclusions follow from the results of the 40-minute infusions. First, that increases in the osmotic pressure of the arterial blood—increases which, when large, were shown by the short-period injections to release post-pituitary antidiuretic substance—are still operative when they are reduced to values well within a range which may reasonably be regarded as physiological. An increase of only 1.8% in the osmotic pressure of the carotid blood gradually reduces the rate of urine flow from a water-diuresis maximum to the sort of rate which prevails at the beginning and end of a normal response to ingested water—i.e., a reduction of some 90%. The smallness of the osmotic pressure increase gains additional interest when it is recollected that the intracarotid infusions were unilateral. For if, as is probable, only half of the total number of osmoreceptors are being exposed under these conditions to the osmotic pressure increment, an increase of some 1% only (54 mm. Hg in absolute terms) in the osmotic pressure of the *aortic* blood would suffice to produce the same degree of inhibition of urine flow—i.e., a reduction to about 10% of the maximum rate of which the kidney is capable during water diuresis.

Secondly, the results of the 40-minute infusions demonstrate that the induced change in the osmotic pressure of the arterial blood which is responsible for this degree of reduction in urine flow itself causes the release of post-pituitary antidiuretic substance at an average rate of 1 μU/sec. (0.5×10^{-9} g./sec. in terms of the standard powder), this being the intermediating agency through which the change in osmotic pressure becomes effective.

Thirdly, the recovery of urine flow when the intracarotid infusion is stopped (Fig. 5) shows that the secretion of post-pituitary antidiuretic substance is now inhibited by the local fall in osmotic pressure and consequent depression of activity in the osmoreceptors, the progression of this recovery being attributable to the gradual destruction in the kidney, and maybe in the blood, of the quantity of anti-diuretic substance which was maintaining the secretion of urine at a non-diuretic level. The latent period between the peak of the water-load curve and the maximum rate of urine secretion, to which I referred earlier and promised to return, is clearly to be attributed to the same process.

Water diuresis, then, is fitly and accurately described as a condition of physiological diabetes insipidus, and there can be little doubt that the antidiuretic secretion of the neurohypophysis is a hormone in the physiological sense that its liberation is mainly and continually governed by the contemporary concentration of sodium chloride in the carotid arterial plasma. The physiological fitness of this control is emphasized by its quantitative aspects, in that changes within the range and of the order of 1% in the osmotic pressure of the arterial blood lead, through the intermediation of the antidiuretic hormone, to changes in the rate of water excretion within the range and of the order of 1,000%: the maintenance of near constancy in the osmotic pressure of the internal environment is thereby achieved.

THE USE OF POST-PITUITARY EXTRACT IN PHYSIOLOGICAL AMOUNTS IN OBSTETRICS

A PRELIMINARY REPORT

BY

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In 1895 Oliver and Schäfer reported that extracts made from the pituitary gland caused a rise of blood pressure in anaesthetized animals when injected intravenously. Three years later Howell (1898) demonstrated that their pressor activity was confined to the posterior lobe, and this was confirmed in the following year by Schäfer and Vincent. In 1901 Schäfer and Magnus reported that post-pituitary extract exerted both diuretic and antidiuretic activities, and it was not until 1915 that Konschegg and Schuster first demonstrated that in conscious animals only an antidiuretic response could be obtained. Dale, in 1906, was the first to draw attention to the fact that this extract stimulated uterine muscle, and this activity was confirmed in 1909 by Frankl-Hochwart and Fröhlich.

It is now generally accepted that post-pituitary extract contains two active principles: (*a*) a pressor which is identical with the antidiuretic activity, and (*b*) an oxytocic substance. Both principles are destroyed by heat, tryptic digestion, hydrochloric acid decomposition, and alkaline hydrolysis, and both are of approximately the same molecular size. Further, in the most purified extracts the pressor and oxytocic activities remain in the same proportions as in an ordinary post-pituitary extract. It was for these reasons that for many years controversy raged on whether post-pituitary extract contained one or more active principles, and it was not until 1928 that Kamm *et al.* settled the dispute by separating and concentrating two active principles in the form of potent solid preparations.

In 1925 a Committee of the League of Nations adopted the U.S.P. Standard Reference Powder as the international standard, 0.5 mg. of this powder being equivalent to one international unit. The international standard preparation of the post-pituitary gland is simply a powder made from the whole posterior lobes of cattle, collected immediately after death and ground in acetone in order to remove water and fat. The different standard powders may therefore differ somewhat in activity, but it is unlikely that the discrepancy ever exceeds 20% in either direction.† Until 1928 post-pituitary extracts were standardized for their oxytocic activity by a method devised by Dale and Laidlaw in 1912, but the separation of two distinct principles by Kamm *et al.* suggested the desirability of devising a separate method for assaying the pressor activity of these extracts.

Blair Bell was the first to use post-pituitary extract in obstetric practice, and in 1909 he reported its efficacy in the treatment of post-partum haemorrhage and intestinal atony. It is of interest to note that before this date no clinical application of

*Mr. Gange terminated his appointment as resident obstetric officer at the end of December, 1947.

†We are greatly indebted to the Director of the Department of Biological Standards, the National Institute for Medical Research, Hampstead, for the above information.

post-pituitary extract had been made other than to prescribe tablets by mouth for their supposed diuretic activity. Two years later Hofbauer (1911) suggested its use in the treatment of uterine inertia. In 1927 Bourne and Burn concluded "that valuable application of a dose of 2 units can be made in cases in which labour is prolonged owing to sluggish pains provided that in primiparae dilatation is nearing completion." There is still, however, a widespread fear, based on unfortunate happenings, of using post-pituitary extracts until labour is completed. Reid (1946) and Eastman (1947) have recently advocated the use of small amounts of post-pituitary extract in cases of prolonged labour. Reid advocates starting with one minim (0.06 ml.) and increasing the dosage to not more than five minims (0.3 ml.), whereas Eastman is more cautious and starts with a half-minim (0.03 ml.), and never gives more than one minim. Both authors consider it wise to confine this method of treatment to obstetrically normal primigravidae whose progress in labour is tedious.

In 1931 Burn described a method of estimating the antidiuretic activity of post-pituitary extract by injecting it subcutaneously into a number of rats. This method was accurate within certain limits, but the subcutaneous route of injection introduced unknown, incalculable, and avoidable errors. Using the method described by Klisiecki *et al.* (1933), one of us (Theobald, 1934a, 1934b) showed that the intravenous injection of from 0.0005 to 0.01 unit of "infundin"* inhibited water diuresis not only in the dog but also in man, and in women during the last few weeks of pregnancy. The amount of antidiuretic activity necessary to inhibit water diuresis was remarkably constant for each dog, and the water diuresis curves thus inhibited, obtained over a period of several months, could be almost superimposed. Later in the same year Bentz, Marx, and Schneider (1934) and Stehle (1934) also showed that very small amounts of post-pituitary extract, when injected intravenously, inhibited water diuresis in the dog.

Two conclusions may be drawn from these results. The first is that, contrary to the observation of Kamm *et al.*, the antidiuretic activity affords the most delicate and possibly the most accurate method of assaying post-pituitary activity. The second is that the post-pituitary gland elaborates the two active substances in remarkably constant proportions (a fact observed by many workers), for it will be noted that infundin is standardized for its oxytocic activity. It was for this reason that it has always seemed to us logical to assume that the normal physiological oxytocic responses in the body are effected by an amount of the oxytocic principle of the same order as that of the antidiuretic principle which inhibits water diuresis.

For the same reasons one of us has postulated (Theobald, 1934b) that the post-pituitary gland does not elaborate a pressor principle, but that the antidiuretic principle, when injected intravenously in many thousand times its physiologically effective amount, happens to exert a transient pressor effect. Further, several observers have reported that post-pituitary extract constricts the coronary vessels, while Leschke (1919) has stated that it causes sino-auricular block, and these concomitant effects can hardly be regarded as desirable or likely to accompany the activity of a physiological pressor substance. We are not aware that Verney has specifically stated that it is illogical to assume that Nature would provide the same substance both to elevate the blood pressure and to inhibit water diuresis, when it is evident that many thousand times the amount adequate for the one activity is required to effect the other, but it is clearly implicit in his writings (Verney, 1947).

Clinical Observations

We have addressed ourselves to two main problems: (1) the induction of labour, and (2) the stimulation of uterine pains in cases of uterine inertia.

The procedure was as follows: Either 9 or 19 ml. of 5% glucose-saline was placed in a small sterile bowl, and to it 1 ml. of "pituitrin"† was added and stirred. The requisite amount of this mixture was then added to a standard bottle containing 500 ml. of a 5% glucose-saline solution prepared for intravenous injection. The dilutions of the pituitrin drip we have used have been 1 in 2,500, 1 in 5,000, and 1 in 10,000. Whereas for some months we used the 1 in 2,500 solution almost exclusively, we now prefer either the 1 in 5,000 or the 1 in 10,000 solution. It may be that the ideal lies in between the last two strengths. There is some reason to believe that the 1 in 2,500 solution occasionally causes irregularity of the foetal heart. In addition to the pituitrin we have sometimes added quinine bihydrochloride 2 gr. (0.13 g.), carbachol 25 mg., and 100–200 mg. of pethidine to the bottle of glucose-saline. The drip was set up in the ordinary manner, using a vein in either the arm or leg, and the infusion was begun at a standard rate of 40 drops to the minute. This rate was decreased if the pains became too strong or too frequent, and was occasionally increased. Not more than three bottles were given on any one day, but the drip was often discontinued and restarted on the following day.

Induction of Labour

It was felt that if a safe, efficient, and reasonably rapid method of inducing labour at any time during the last three weeks of pregnancy could be devised it would be of distinct value in obstetrics. It can be stated that, so far, the pituitrin drip, even when quinine and carbachol were added, proved a quite unreliable method of terminating pregnancy, and failed more often than it succeeded.

We found that the most effective single method of inducing labour was to sweep the membranes from that part of the lower uterine segment immediately above the internal os uteri with the finger and to touch this denuded area lightly with the silver stick. Labour supervened within 24 hours in the first 11 cases, but subsequent experience showed that the method was not always successful.

The routine to which we adhere at present is composite. In the first instance, four doses of quinine sulphate 10 gr. (0.65 g.) are given at four-hourly intervals. Two ounces (57 ml.) of castor oil are given either just before or just after the third dose of quinine. A copious warm enema is administered approximately four hours after the castor oil. If the woman does not go into labour within 24 hours from the time that the quinine induction is completed the membranes are ruptured at a point immediately below the presenting part. Should she not go into labour during the next 24 hours the pituitrin drip is started.

During the first three months of this year 43 patients were subjected to this method of induction of labour. Twenty-two went into labour within 24 hours of the completion of the quinine therapy; the membranes were ruptured in 20 cases; and the pituitrin drip was administered in 9 cases. In one of these the pituitrin drip was given 24 hours after the completion of the quinine therapy. The membranes of this patient were not ruptured, because she showed a marked degree of pelvic contraction. All the infants, save one, a breech delivery, were born alive and survived. One of us (G. W. T.) has used the quinine method of induction in hundreds of cases; we are satisfied that it is a safe way to induce labour, and it is successful in between 50 and 60% of all cases at term. The intervals between the administration of quinine must not be less than four hours, and the drug must be withheld once uterine contractions begin. In our experience any other form of medical induction is comparatively unsuccessful.

Only two patients caused anxiety, and they were both elderly obese multigravidae. Subsequent labour was in each case associated with marked uterine inertia. One was a 5-gravida, aged 35, with hypertension, who had not been pregnant for some years and was overdue; the other was a 6-gravida, aged 45, whose first pregnancy had terminated by caesarean section and whose youngest child was 6 years old. In each case delivery was effected by a difficult forceps extraction. The infant of the former patient died as the result of cerebral haemorrhage.

A number of patients were admitted after spontaneous rupture of the membranes. In our experience labour may be delayed subsequent to the rupture of the membranes for as many as eight days, and this delay may be associated with intrauterine death of the foetus. In these cases a pituitrin drip, containing in addition quinine hydrochloride 2 gr. (0.13 g.) in

*A commercial preparation of post-pituitary extract made by Messrs. Burroughs, Wellcome and Co., and standardized for its oxytocic content.

†A commercial preparation of post-pituitary extract made by Messrs. Parke, Davis and Co., and standardized for its oxytocic content.

each bottle of glucose-saline solution, is set up. The drip is taken down after two or three bottles have been administered and recommenced next day. Whereas the drip may have no apparent effect on the first day, it usually happens that uterine contractions occur within one to ten minutes of restarting the drip on the following day.

It is our practice to rupture the membranes whenever possible in the treatment of placenta praevia and to apply a tight binder. In three recent cases labour did not supervene within the course of the next 20 hours, so the pituitrin-quinine drip was begun. In one case labour pains started almost immediately, while in the other two it had to be repeated next day. All these babies were born alive and well.

Primary Uterine Inertia

We first treated cases of primary uterine inertia by the pituitrin drip method in June, 1947, and propose to report the results obtained in 20 consecutive cases treated during the last 5 months. Only one of these patients had previously given birth to a full-term living child *per vias naturales*, and she was a 5-gravida. Two had previously been delivered by caesarean section, and one had had two miscarriages and a premature infant which had died. Of the 20 patients four were aged 40 years or over and nine were over 30 years (three being 38 years old). In nine cases the head was free above the brim, and in only four was the head fully engaged. One was a breech presentation. After "trial labours" two were delivered by caesarean section. Nine patients were delivered by the forceps, and the remaining nine delivered themselves spontaneously. One baby died from a tentorial tear. The largest infant weighed 9 lb. (4.08 kg.), and the average weight was 7 lb. 6 oz. (3.34 kg.).

Case Reports

Case 1 : Placenta Praevia.—D.M., aged 23; 1-gravida; term. *Nov. 16, 1947 :*—Admitted because of ante-partum haemorrhage; not in labour. *Nov. 17:*—7 p.m.: Cervix two fingers dilated; marginal placenta praevia; membranes ruptured; Willett's forceps applied to control bleeding. 9.30 p.m.: Weak pains at five-minute intervals. *Nov. 18:*—1 a.m.: Weak pains every 15 minutes. 3 a.m.: No pains. 9.30 a.m.: Still no pains. 10.10 a.m.: Pituitrin 1 in 2,500 + quinine 2 gr. (0.13 g.) drip begun. 10.20 a.m.: Slight short pain. 10.30 a.m.: Moderate pains every three minutes; drip stopped; 1/3 pint (190 ml.) given. 12.40 p.m.: Cervix fully dilated. 1.30 p.m.: Delivery of living female child weighing 7 lb. 8 oz. (3.4 kg.). 1.48 p.m.: Placenta and membranes expelled complete.

Case 2: Induction of Labour.—E.H., aged 23; 2-gravida; term; previous elective classical caesarean section for contracted pelvis associated with transverse lie. *Sept. 30, 1947:*—12.30 a.m.: Membranes ruptured. 1 a.m.: Admitted to hospital; transverse lie; no pains; draining liquor amnii; lie changed to vertex by external manipulation; pads and binder applied. 7 p.m.: Still no pains—head free; pituitrin 1 in 2,500 + quinine 2 gr. drip. 7.45 p.m.: Vague pains—one every 20 minutes. 9 p.m.: Moderate pains every five minutes; head engaging. 10 p.m.: Second bottle started. 11 p.m.: Head on perineum; drip discontinued. *Oct. 1:*—1.17 a.m.: Spontaneous delivery of living male child weighing 6 lb. 7 oz. (2.92 kg.).

Case 3 : Induction of Labour.—A.S., aged 31; 1-gravida. *June 8, 1947:*—11 a.m.: Membranes ruptured. *June 9:*—7 p.m.: Admitted to hospital; no pains. 8 p.m.: Head engaging; os two fingers dilated; B.P. 130/70 mm. Hg. 8.35 p.m.: 1 in 5,000 pituitrin drip started (30 drops a minute). 11.35 p.m.: Pains every 5 minutes—fairly strong; os two fingers dilated; drip slowed to 20 drops a minute; pot. brom. and chloral hydrate āā 30 gr. (2 g.). *June 10:*—1.15 a.m.: Os fully dilated. 2.10 a.m.: Spontaneous delivery of living female child, 6 lb. 5 oz. (2.86 kg.).

Case 4 : Induction of Labour; Uterine Inertia.—M.H., aged 40; 1-gravida; 38 weeks. *Sept. 8, 1947:*—Admitted with hypertension. *Sept. 17 :*—11.50 a.m.: Pituitrin 1 in 2,500 + quinine 2 gr. drip started (three bottles given). *Sept. 18:*—5.30 p.m.: Pains began. 6.30 p.m.: Membranes ruptured. 7.10 p.m.: Moderate pains every 10 minutes; head engaged; os two fingers dilated. 8.40 p.m.: Pains every four minutes—strong; os two to three fingers dilated; pethidine 150 mg. and hyoscine 1/100 gr. (0.65 mg.) given. 10 p.m.: Sleeping. *Sept. 19:* 12.40 a.m.: Strong pains every three minutes; no progress. 11.20 a.m.: Still no progress. 1.15 p.m.: Pituitrin 1 in 5,000 + quinine 1 gr. (65 mg.) drip started; B.P. 155/110 mm. Hg. 2.35 p.m.: Needle out of vein; drip discontinued; indefinite pains. 4 p.m.: Second bottle of pituitrin+quinine drip started. 5 p.m.: Moderate pains every four minutes. 6 p.m.: Mild rigor. 6.40 p.m.: Strong pains every four minutes. 8.30 p.m.: Strong pains every four minutes; os three to four fingers dilated. 10.50 p.m.: Only rim of cervix palpated; pethidine 100 mg. given. *Sept. 20:*—5.20 a.m.: Forceps delivery of living female child 7 lb. 10 oz. (3.46 kg.).

Case 5 : Induction of Labour; Uterine Inertia.—C.G., aged 21; 1-gravida. *Nov. 26, 1947:*—Membranes ruptured spontaneously during the night. *Nov. 27:*—5.15 p.m.: Admitted to hospital. *Nov. 28:*—10 a.m.: No pains; no obvious loss of liquor amnii. 3.50 p.m.: Draining much liquor amnii; no pains. 9.5 p.m.: Foetal heart 120, irregular; no pains. 11.10 p.m.; Pituitrin 1 in 2,500 + quinine 2 gr. drip started. 11.15 p.m.: B.P. 104/60 mm. Hg; no pains. *Nov. 29:*—12.10 a.m.; no pains. 12.40 a.m.: Pot. brom. and chloral hydrate āā 30 gr. (2 g.) given. 1 a.m.: Second bottle of pituitrin drip started. 2.45 a.m.: Weak pains every 10 minutes. 3.30 a.m.: Third bottle started. 5.10 a.m.: Drip discontinued; foetal heart 120, regular; castor oil 2 oz. (57 ml.) given, followed four hours later by enema. 10.10 a.m.: Fairly strong pains every five minutes; head free; os one finger dilated. 2.10 p.m.: Moderate pains every 10 minutes; head free. 7.35 p.m.: Pelvis contracted, but no obvious disproportion; pot. brom. and chloral hydrate āā 30 gr. given. *Nov. 30:*—12.15 a.m.: Weak pains; pot. brom. and chloral hydrate āā 30 gr. repeated at 2 a.m. 10.50 a.m.: Slept well; no pains; head still free; liquor amnii blood-stained. 11.45 a.m.: Pituitrin 1 in 2,500 + quinine 2 gr. drip started; B.P. 104/60 mm. Hg; pains started immediately; uterine spasm; drip slowed for 10 minutes. 12.15 p.m.: Strong pains every three minutes; foetal heart rate 136. 12.45 p.m.: Needle out of vein. 1.45 p.m.: Drip restarted; head engaging; os two fingers dilated. 2 p.m.: Strong pains every three minutes; pot. brom. and chloral hydrate āā 30 gr. 2.20 p.m.: Pethidine 100 mg. and hyoscine 1/150 gr. (0.433 mg.) given. 3.45 p.m.: Well sedated. 6.15 p.m.: Third bottle started; strong pains every three minutes; head still palpable above brim. 6.30 p.m.: Drip discontinued. 7 p.m. : Head showing at vulva. 7.10 p.m.: Spontaneous delivery of living female child, 6 lb. 1 oz. (2.75 kg.).

Case 6 : Uterine Inertia.—A.B., aged 43; 5-gravida; 39 weeks. *Feb. 14, 1948 :*—5.10 a.m.: Membranes ruptured. 12 midnight: Labour started. *Feb. 15:*—6 a.m.: Admitted to hospital; head free; cervix closed; pains moderate. *Feb. 16 :*—10 a.m.: Head entering pelvic inlet; cervix one finger dilated; pains weak. 4.30 p.m.: Pains stronger, every two to three minutes. 5.15 p.m.: Cervix one finger dilated; morphine 1/4 gr. (16 mg.), scopolamine 1/100 gr. (0.65 mg.), nembutal 1½ gr. (0.1 g.). 6.15 p.m.: Pituitrin drip 1 in 10,000 begun; B.P. 108/80 mm. Hg. 6.55 p.m.: Pains stronger. 8 p.m.: Pains strong; cervix two fingers dilated; B.P. 110/80 mm. Hg. 10 p.m.: Pains strong; head descending; cervix 3/4 dilated; drip stopped. 10.45 p.m.: Precipitate delivery of living child.

Case 7 : Uterine Inertia; Incision of Cervix.—L.S., aged 31; 1-gravida; term. *Nov. 20, 1947 :*—Admitted at 9.30 p.m. from a nursing-home with history of having started labour at 9 p.m. on Nov. 16 and membranes having ruptured at 5 a.m. on Nov. 17. On admission the head was well engaged; os one finger dilated; B.P. 145/100 mm. Hg. Morphine 1/4 gr. was given immediately. *Nov. 21 :*—7 a.m.: Irregular pains at approximately ten-minute intervals. 2.30 p.m.: Moderately strong pains every three minutes; pethidine 100 mg. 3.30 p.m.: Pethidine 100 mg. 8 p.m.: Strong pains every five minutes. 11.45 p.m.: Pethidine 200 mg. given. 12 midnight: Pituitrin 1 in 2,500 + quinine 2 gr. drip started; B.P. 140/100 mm. Hg. *Nov. 22 :*—12.45 a.m.: Pains every seven minutes; B.P. 140/100 mm. Hg. 2 a.m.: Strong pains every five minutes. 2.5 a.m.: Pethidine 100 mg. given. 4 a.m.: Pains still strong; no change in position of head; os two fingers dilated. 9.30 a.m.: Drip discontinued. 11 a.m.: Has slept well since 5 a.m.; condition good. 1.20 p.m.: Cervix incised and living female child weighing 8 lb. (3.63 kg.) delivered with forceps. Post-partum haemorrhage controlled with ergometrine.

This patient was in labour for nearly six days, and although the cervix became thinned out, it failed to become more than half dilated in spite of fairly good pains.

Case 8 : Uterine Inertia.—M.L., aged 38; 1-gravida; term. *Jan. 9, 1948 :*—11.30 p.m.: Admitted to hospital, membranes having ruptured. *Jan. 10 :*—12 noon: Vague uterine contractions; head free; cervix closed. 5 p.m.: Pains as they were; os one finger dilated; head just tipped. 6.45 p.m.: Pituitrin 1 in 2,500 + quinine 4 gr. (0.26 g.) started; B.P. 150/110 mm. Hg. 7.45 p.m.: Patient vomited profusely; weak contractions every five minutes; head descending; os almost two fingers dilated. 10 p.m.: Continuous backache; contractions as before; head advancing; os three fingers dilated; pethidine 100 mg. given. 11.15 p.m.: Drip discontinued; one bottle given; morphine 1/4 gr., hyoscine 1/100 gr. given; slept well most of night. *Jan. 11 :*—12 noon: Vague uterine contractions; slight backache; B.P. 150/110 mm. Hg; os three fingers dilated. 12.15 p.m.: Pituitrin 1 in 2,500 + quinine 2 gr. drip restarted. 2.15 p.m.: Weak contractions every five minutes; head in mid-cavity; os three fingers dilated; B.P. 150/90 mm. Hg. 3.30 p.m.: Second bottle begun; pains every ten minutes; B.P. 170/110

mm. Hg; os three to four fingers dilated; head in same position. 5.30 p.m.: Strong contractions every five minutes; B.P. 140/90 mm. Hg; os 3/4 dilated; pethidine 100 mg. given. 8.30 p.m.: Strong contractions every five minutes; rim of cervix only palpated anteriorly; pethidine 100 mg. given. 9.30 p.m.: Third bottle begun; B.P. 140/90 mm. Hg; general condition good. *Jan. 12:*—6 a.m.: Still small rim of cervix anteriorly; pethidine 100 mg. given; slept well. 11.30 a.m.: Second stage begun. 2.12 p.m.: Forceps delivery of living female child, 9 lb. (4.08 kg.).

Case 9 : Uterine Inertia.—M.F., aged 20; 1-gravida; 41 weeks. *Sept. 15, 1947:*—5 a.m.: Pains started. 6 a.m.: Admitted to hospital. 9.40 a.m.: Pains irregular; membranes intact; head engaging; os one finger dilated. 4.30 p.m.: Weak pains every 20 minutes; membranes intact; no progress. 11.30 p.m.: Pot. brom. and chloral hydrate āā 30 gr. *Sept. 16:*—10 a.m.: Pains stronger—every six minutes; head engaged; os one finger dilated. 2 p.m.: Pains fairly strong; no progress. 5 p.m.: No progress; pains weak; pituitrin + quinine 2 gr. + pethidine 150 mg. drip. 5.55 p.m.: Pains stronger—every 5 minutes. 7.30 p.m.: Os two fingers dilated. 8.45 p.m.: Pains strong; os three fingers dilated; pethidine 100 mg. 8.55 p.m.: Second bottle started. 10.33 p.m.: Spontaneous delivery of a living male child, 7 lb. 11 oz. (3.49 kg.).

Discussion

The pituitrin drip may cause no uterine contractions if the woman is not in labour, and on the other hand may cause strong uterine contractions within five minutes, even within one minute, of its commencement. We have come to the conclusion that a 1 in 2,500 solution is too strong, and that the optimum dilution possibly lies between 1 in 5,000 and 1 in 10,000 of the post-pituitary extract. Kamm *et al.* (1928) stated that they had prepared post-pituitary extracts having an oxytocic activity 150 times greater than that of the standard powder, and later writers have made similar claims (Stehle and Fraser, 1935 ; Du Vigneaud *et al.*, 1933). None of these authors claims to have isolated the oxytocic principle in pure form, so that it is reasonable to assume that the post-pituitary oxytocic principle possesses an oxytocic activity at least 150 times greater than that of the international standard powder. Let it therefore be assumed (*a*) that the post-pituitary gland elaborates an oxytocic principle at least 150 times more potent than that of the standard powder ; (*b*) that the average pregnant woman possesses three litres of blood plasma ; (*c*) that none of the oxytocic activity becomes adsorbed to the red blood corpuscles ; and (*d*) that labour pains do not start until after the drip has been running for five minutes, during which time $\frac{200}{17}$, or 12 ml., of the drip has entered the blood stream: it would then follow that a concentration of the oxytocic principle in the blood plasma not exceeding 1 in $\frac{10,000}{12} \times 3,000 \times 150 = 1 : 375 \times 10^6$ may suffice to initiate or to stimulate uterine pains.

In those cases in which spontaneous rupture of the membranes occurs before the onset of labour we consider it desirable to add 2 gr. of quinine hydrochloride to each bottle of glucose-saline solution in addition to the post-pituitary extract. If uterine contractions do not occur it is probably desirable to take down the drip after two bottles have been given and to restart it on the following day. In such cases it often happens that strong pains occur immediately the drip is recommenced.

The pituitrin drip does not cause a woman suffering from uterine inertia to have very strong pains, but it does in almost every case increase both the frequency and the intensity of the pains. An elderly primigravida may be in labour for three days and longer without any advance of the presenting part and without any dilatation of the external os. The pains, although ineffective, suffice to exhaust her. Morphine and other drugs potent enough to afford the woman adequate rest tend to put her "out of labour." The pituitrin drip is invaluable in such cases and makes possible the use of morphine and pethidine, for the drip can be continued while the patient is adequately narcotized. If we had to choose between the narcotic drugs and the pituitrin drip we should unhesitatingly choose the former, but we believe the drip to be a very valuable aid in the treatment of these peculiarly difficult cases.

The uterus apparently relaxes completely between the pains stimulated by the pituitrin drip. Slight irregularities in the foetal heart were noted occasionally, particularly when the 1 in 2,500 pituitrin drip was used. In such cases the drip was slowed. No permanent adverse effects on the foetus were observed. We consider it perfectly safe to use the pituitrin drip in cases of contracted pelvis when the head is not engaged, in cases of hypertension, and in cases of placenta praevia. It will be seen that Case 2 was previously delivered by a classical caesarean section. We no longer consider it safe to allow such patients to undergo trial labour, and for this reason we regard it as unsafe to administer the pituitrin drip to such cases. We know of no other contraindication to the use of the pituitrin drip provided it is thought desirable to stimulate the uterine pains.

Schockaert and Lambillon (1937) showed that the intravenous injection of "tonephin" (a post-pituitary pressor preparation) caused a higher and more prolonged rise in the blood pressure of patients suffering from "pre-eclamptic toxaemia" than in normal pregnant women, and these findings have been confirmed by de Valera and Kellar (1938) and by Browne (1944). The pituitrin drip causes no elevation of the blood pressure in normal patients, but a rise is sometimes detected in patients suffering from hypertension (see Case 9). The elevation is usually temporary, and strictly similar rises have been noted when a 1 in 10,000 dilution of "pitocin" * was used. We propose in a subsequent paper to discuss this matter more fully, to record the antidiuretic effects, and to reproduce kymographic tracings of the uterine contractions caused by the pituitrin drip.

Summary

A dilution of the oxytocic principle of post-pituitary extract in the blood plasma of an order not exceeding $1 : 375 \times 10^6$ is capable both of initiating and of augmenting labour pains in man. This dilution is comparable to that of the antidiuretic principle which suffices to inhibit water diuresis. This evidence makes it increasingly difficult to believe that the post-pituitary gland is normally concerned either with regulating or with elevating the blood pressure.

The use of the pituitrin-quinine drip is of great value in those cases in which the woman fails to go into labour subsequent to the rupture of the membranes, whether spontaneously or as the result of surgical intervention.

The pituitrin drip increases both the frequency and the intensity of the uterine pains in cases of uterine inertia and makes possible the adequate use of sedative drugs in the conduct of the labour.

The pituitrin drip may be used in all cases in which it is considered desirable and safe to stimulate the uterine pains, and it is immaterial whether the woman is a primigravida or a multigravida, whether or not she suffers from hypertension, or whether the head is above the brim.

It is not impossible that it will be found advantageous to apply the pituitrin drip to a wider range of cases. It is also possible that it will find a place in the third stage of labour, particularly in those cases of severe post-partum haemorrhage in which the placenta is retained. The pituitrin would of course be added to the transfused blood.

We have in the majority of cases used pituitrin, but pitocin would appear to be equally efficacious, and it would perhaps be more logical to use the latter preparation, particularly in those cases which manifest hypertension.

*A commercial preparation of the oxytocic principle of the post-pituitary gland prepared by Messrs. Parke, Davis and Co.

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SUBTOTAL COLECTOMY AND COLECTOMY IN ULCERATIVE COLITIS

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The treatment of ulcerative colitis in this country has always been regarded as medical. Like most Australian surgeons, we have had little experience of the surgical treatment of this condition because patients suffering from ulcerative colitis are only referred for surgical treatment as a last resource. In three metropolitan hospitals over a ten-year period, the Royal Melbourne (in this hospital the ten-year period did not include the last two years), the Alfred, and St. Vincent's, 341 patients suffering from ulcerative colitis were admitted. Of these, 87 died and 23 were treated surgically (in one hospital 3 cases, in another 5, and in a third 15). There were 6 cases of appendicostomy, 6 of ileostomy, 5 of colostomy, 1 of ileosigmoidostomy, 1 of ileocolostomy, and 1 of colectomy. Of the 6 patients subjected to enterostomy 5 died.*

From these figures we may infer that in Victoria the incidence of ulcerative colitis is material; that its treatment has been mostly medical and has not been very successful; and that what little surgical treatment has been practised has not been of much value. This paper is founded on a relatively small series of cases, but they were desperate ones, and the later cases reflect team work by the authors—a necessary method of work in this critical surgery which demands painstaking and scientific preparation, often synchronous operating, small bedside operations, skilful post-operative methods, and constant surgical attention. Our interest in the radical surgical treatment of this condition was awakened by a particularly bad case which came under our notice (H.B.D.) in 1941.

Case 1.—A woman aged 34, who had been ill for six months with obscure abdominal symptoms, a progressive secondary anaemia, and some disturbance of her bowel function, became acutely ill with severe abdominal pain. She was operated on in the belief that she had an acute appendicitis; the appendix appeared acutely inflamed. About a week after the operation she began to have frequent and painful bowel actions and to pass large quantities of blood with some pus. It was apparent that she had a fulminating ulcerative colitis. Sigmoidoscopy confirmed this diagnosis and showed that the rectum was also badly affected. Notwithstanding many blood transfusions and every kind of treatment she steadily got worse until she was emaciated, cachectic, exhausted, and almost moribund.

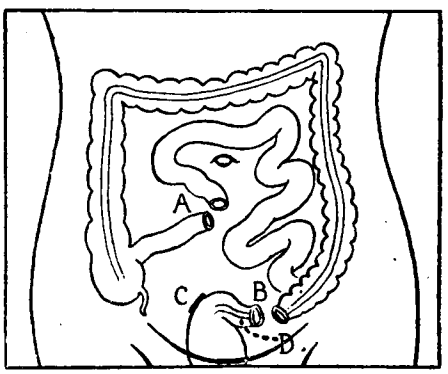

FIG. 1.—A=divided ileum; B=divided sigmoid; C=some mobilization of rectum; D=some prolapse of peritoneum of anterior abdominal wall around the sigmoid remnant so that when the bowel-ends are being closed the size of the sigmoid remnant can be reduced by amputation.

Conservative surgical measures such as appendicostomy or enterostomy could offer little hope of cure and she was too weak to stand a colectomy. We decided therefore on a "piecemeal" surgical approach, each successive step in treatment being designed not only to bring about improvement but also to be a stage in the removal of the colon. (*a*) An enterostomy was so planned that it was a step in the formation of an ileorectostomy (Figs. 1 and 2).

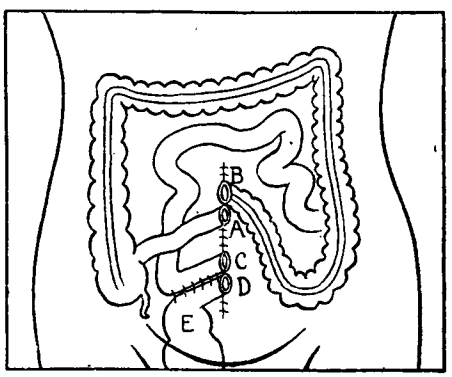

FIG. 2.—A=distal end of the ileum; B=distal sigmoid; C and D show the ileosigmoid spur made up of proximal end of ileum and distal end of sigmoid; E=rectum.

(*b*) About five weeks later the ileum was connected to the rectum by the use of a special spur-clamp (Fig. 3) and the open ends of the bowel taking part in the anastomosis were closed under local anaesthesia (Figs. 4 and 5). (*c*) The colon, now isolated, with both ends open forming two mucous fistulae, was completely out of action and was treated by routine chemotherapy over a period of months until the patient ceased to improve. Since she had no discharging enterostomy and was comparatively comfortable, the length of this period was immaterial and we could wait almost any time (in this case eight months) till we felt that she was thoroughly

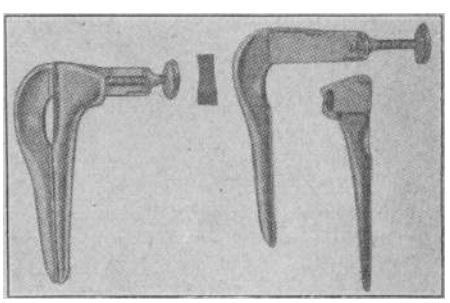

FIG. 3

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