ENDOCRINES IN THEORY AND PRACTICE

This article is one of a series on Endocrinology contributed by invitation

THE HORMONE TREATMENT OF SOME DISORDERS OF PREGNANCY

BY

T. N. A. JEFFCOATE, M.D., F.R.C.S. Ed.

PART II

Missed Abortion, Carneous Mole, and Intra-uterine Death of the Foetus

These interesting conditions are essentially the same in so far as the ovum or foetus dies but remains *in utero* because the normal stimulus to uterine action is lacking. Oftentimes evacuation of the uterus eventually takes place spontaneously, but occasionally weeks or months elapse without there being any sign of the onset of expulsive uterine contractions. In such cases artificial evacuation of the uterus is indicated, and it is for this purpose that oestrogenic hormone is useful. The ordinary medicinal induction generally fails because the uterus is not sufficiently sensitive to respond. The continued administration of oestrogenic hormone, however, increases uterine activity to such an extent that even if evacuation does not take place spontaneously the uterine contents are at once expelled when oxytocic drugs are given. The following technique is successful in at least 80 per cent. of cases.

Oestradiol benzoate, 40,000 international benzoate units (200,000 international units), should be injected intramuscularly every eight hours for eight days (unless evacuation takes place before the elapse of that time). On the fifth day quinine and pituitary induction, using the technique outlined previously, should be carried out. The administration of oestrus-producing hormone should be continued throughout, and if the first attempt at medicinal induction fails the quinine and pituitary should be repeated as before on the eighth or ninth day. Only on the rare occasions when the uterus fails to respond to this treatment is it necessary to institute operative measures. In actual practice the oestrogenic hormone frequently brings about the desired result without further uterine stimulants being necessary: this is especially true if the pregnancy is far advanced and the foetus has been dead for a relatively short period of time. This form of treatment is of no value for "incomplete abortion"; in this condition the residual fragments of placenta or membranes are usually adherent to the uterine wall.

It is at first sight rather remarkable that hormonal evacuation of the uterus is rendered possible by the death and retention of the foetus. It is, however, now known that in these cases the amount of oestrin in the blood is considerably reduced, or, alternatively, is present in a "combined" and inactive state. So characteristic is this feature that if less than 1 mouse unit of active oestrogenic substance is demonstrable in 40 c.cm. of blood the diagnosis of foetal death can be made. This test is more reliable than radiological or clinical investigation.

The rationale of treatment is therefore clear: the administration of preparations having oestrogenic properties remedies a pre-existing deficiency in the blood stream.

Excessive Vomiting and Toxaemia of Pregnancy

For many years past one of the theories of the aetiology of hyperemesis gravidarum has depended upon a supposed defective function on the part of the corpus luteum, and acting on this supposition many clinicians have prescribed corpus luteum tablets for this distressing complaint. The impotence of such tablets, from the hormonal standpoint, has already been emphasized. Since the theory on which the treatment is based has never been substantiated by pathological evidence the administration of even standardized preparations of progesterin is not recommended as a means of controlling pernicious vomiting.

It has recently been suggested that in cases of pregnancy toxaemia there is a relatively excessive amount of prolan and a deficiency of oestrin in the urine. In view of this the administration of oestrogenic hormone for toxaemia of pregnancy is already advocated in commercial literature. The evidence upon which this view of the pathogenesis of toxaemia is based is flimsy and unconvincing, and this form of organotherapy is not advised.

Uterine Inertia

USE OF OESTROGENIC HORMONES

Since the activity of a uterus is primarily dependent on the effect of oestrin many cases of uterine inertia in labour are probably due to a defective supply of this hormone. This suggestion is conjectural, since it has never been confirmed or disproved by hormonal estimations. The deficiency in oestrogenic factors is not necessarily absolute but may be relative; in other words they may be present, but in an inactive state, in the blood stream. This theory has led to a trial of oestrogenic hormone therapy for uterine inertia. Most writers report poor results—on a very small series of cases. In my experience the results are variable, some disappointing and others remarkably good; this is to be expected in view of the numerous and widely different possible causes of defective uterine action. No definite subdivision of cases is yet possible, but it would appear that the results are poor if the inertia is due to emotional influences, local lesions of the uterus, disproportion, or malpresentations. Moreover, the injection of oestrogenic hormone rarely evokes a response in the presence of conditions such as "occipito-posterior position," in which slow dilatation of the cervix and weak contractions in the early stages of labour are beneficial to the patient and the inertia is "physiological" in type.

Primary inertia is more amenable to this treatment than is secondary, and 50 per cent. of all cases of uterine inertia appear to derive some benefit from the administration of oestrogenic substances; in some patients the effect is dramatic. The following technique is advised: 20,000 international benzoate units (or 100,000 international units) of oestrogenic hormone should be injected intramuscularly every hour for at least ten injections, unless the delivery is completed in a shorter space of time. An immediate response is not to be expected, and repeated injections are usually required before any improvement in uterine action is manifested. Occasionally efficient "pains" begin within ten to fifteen minutes after injection, but it has yet to be proved that such a rapid effect is strictly hormonal in origin. It is necessary to empha-

size that this form of therapy is at present on trial only: it has, however, the great advantage of being free from all the dangers that are associated with the administration of other oxytocic substances, and no harm to either mother or child can follow its use. The occasional good results justify its extended employment. Here again hormone therapy should not replace the more established methods of treatment; it should be regarded as additional treatment and should be given when the patient has been rested and refreshed by the use of morphine, which still remains the first and best line of attack in uterine inertia.

From what has been said it is clear that oestrogenic hormone therapy also opens up new possibilities with regard to prophylaxis against inertia. It may prove even more valuable in this respect. When the history of inertia in previous labours, or the detection of an atonic uterus ante-natally, makes the expulsive capacity of a uterus "suspect," 20,000 international benzoate units (100,000 international units) of oestrin should be injected intramuscularly twice daily for two or three weeks before the expected date of delivery.

USE OF POSTERIOR PITUITARY HORMONE

As prophylaxis against inertia 5 units of posterior pituitary should be injected twice daily for two weeks before the expected onset of labour; this treatment is attended with happy results and is devoid of risk. But when labour has started and inertia is established the administration of this hormone requires the utmost caution. The effect of even small doses may be so pronounced that the uterus, cervix, or other soft maternal tissues may be ruptured; moreover, the foetus is likely to die from interference to the placental circulation. Only when the position of the foetus is normal, and when the presence of even mild disproportion is excluded, should the use of posterior pituitary extract be contemplated. Its application is occasionally indicated for patients suffering from accidental ante-partum haemorrhage complicated by defective uterine action. The dose should never exceed 2 units initially, and after its injection the medical attendant should remain with the patient until delivery is complete.

Only rarely is the use of such a powerful oxytocic substance required, and its margin of safety is so small that many obstetricians are coming to regard its employment during labour as unjustified in all circumstances. It is, however, stated that its dangers are somewhat decreased if it is applied intranasally rather than parenterally.

Post-partum Haemorrhage

During the third stage of labour the injection of pituitary extract is dangerous because of its propensity for producing hour-glass contraction of the uterus; it should never be used for third-stage haemorrhage nor to hasten placental separation. But for bleeding occurring after delivery of the placenta this hormone is a life-saving principle and its administration should never be neglected. The intragluteal injection of .5 or 10 units is as a rule sufficient, but 2 units intravenously or 5 units into the uterine muscle (via the abdominal wall) exert a more rapid and certain oxytocic effect, and should be given when control of the haemorrhage is difficult or delayed.

Delayed Involution

When, after abortion or labour, involution is slow and the lochia profuse, and particularly if there is reason to suspect the retention of blood clot or small pieces of membrane in the uterus, 5 units of posterior pituitary extract should be injected intramuscularly twice daily for a few days.

Tonic Uterine Contraction

Tonic uterine contraction may involve the whole of the upper segment, as in obstructed labour, or, on the other hand, it may affect a strictly localized area of one or other segment of the uterus and appear in the form of a "contraction ring." These serious obstetrical complications demand the immediate institution of measures designed to relieve spasm and to reduce uterine tone. Morphine and general anaesthesia do not always have the desired effect, and now that it is claimed that progestin, when given in large doses, quickly exercises an inhibitory action upon the human uterus (puerperal), this hormone should be tried in such conditions. So far I have failed to influence the uterine contractions of *normal* parturition with large doses of progestin (20 international units), but this does not necessarily mean that pathological uterine spasm will not respond favourably to such treatment.

Another endocrinous preparation sometimes advised for tonic uterine contraction is 5 minims of adrenaline hydrochloride 1 in 1,000. The internal secretion of the suprarenal has very varied effects on uterine muscle, and whereas in some patients it temporarily suppresses contractions, in others it produces an opposite response. This treatment is therefore of small value.

The Relief of "After-pains"

Uterine contractions during the first week after delivery are, on occasion, so painful as to cause the patient considerable distress. It is reported that 1 rabbit unit of progestin, by inhibiting the uterus, relieves such pain within fifteen minutes in nearly 90 per cent. of cases. It is, moreover, rarely necessary to repeat the injection. I have no personal experience of this use of progestin, and it is extremely doubtful whether it is wise to allay muscle contractions whose purpose is to expel blood clot and necrotic shreds of decidua and membrane from the uterine cavity. Such contractions are essentially protective in character and should be encouraged rather than suppressed; the injection of 0.5 c.cm. of posterior pituitary extract frequently relieves "after-pains," since it replaces irregular uterine spasm by rhythmical strong contractions.

Disorders of Lactation

Although breast development is brought about by oestrogenic and corpus luteum hormones, the secretion of milk can only be effected through the agency of the anterior lobe of the pituitary—by a special hormone designated "prolactin." This hormone has been given to patients in whom the supply of milk was deficient; the dose so far recommended on empirical grounds is 150 bird units, followed by 100 bird units in twelve to twenty-four hours. Although the rationale of this method is sound the reported results are, so far, discordant, and the usefulness of the hormone in this sphere is at present unproved.

The oestrogenic hormone, while stimulating breast development, inhibits the secretion of milk by its action on the pituitary gland. Hence, in patients in whom lactation is not desirable, the discomfort of engorged and painful breasts is theoretically avoidable by injections of oestrogenic hormone. The dose advised is 10,000 international benzoate units (50,000 international units) of oestrogenic hormone on three successive days, beginning as early as possible after delivery. Although good results are reported for this form of organotherapy I have failed to notice beneficial effects with this dosage. Possibly larger amounts of hormone, continued for a longer period and followed eventually by a gradual reduction in the oestrin supply, would be more efficacious; such a technique has a more scientific basis. It is, however, open

to question whether the discomfort of repeated intramuscular injections is preferable to the pain of engorged breasts, especially since the latter is of short duration and may readily be relieved by other well-recognized methods of treatment.

Dangers of Hormone Therapy

So far as is known at present the administration for short periods of time of the largest doses of oestrogenic, corpus luteum, and gonadotropic hormones is free from risk. But posterior pituitary extracts differ from preparations of the other hormones in that they are extremely dangerous unless prescribed with caution. The possibility of the production of ruptured uterus and tonic uterine contraction by means of these agents has already been discussed. In addition, it should be remembered that most extracts contain a vasopressor factor, and their employment is therefore contraindicated in patients suffering from cardiac disease or toxæmia of pregnancy. Cases are recorded in which the onset of eclamptic fits appears to have been due to such preparations. Moreover, some patients show an idiosyncrasy to pituitary extract, and after receiving it may collapse and present the signs of so-called "pituitrin shock." If this occurs in a patient already suffering from loss of blood the issue may be fatal. It is probable that many cases of "obstetric shock" would be more correctly diagnosed "pituitrin shock."

In view of the above disadvantages and dangers many authorities now advise the use of the isolated oxytocic fraction of the posterior pituitary lobe (for example, pitocin, Parke, Davis and Co.) rather than preparations containing both oxytocic and vasopressor factors. Pitocin possesses a further advantage since its administration does not produce a refractory phase in the uterus, whereas injections of extracts such as pituitrin render the uterus incapable of responding to a second application of the same substance until half to one hour has elapsed. Nevertheless pitocin is equally dangerous when given in labour, although it has a less powerful oxytocic action than have the "mixed" extracts of the posterior hypophysis.

Conclusion

The value and limitations of posterior pituitary hormone therapy are clearly defined, but it is difficult to assess the merit of other forms of organotherapy in the obscure functional disorders of gestation. Any experiments or results must of necessity be uncontrolled, and only by the collection of large numbers of cases can an estimate of the worth of any particular method be made. Nevertheless progress is being made, and already hormones are proving of definite clinical value in some of the conditions mentioned. Their use, however, is strictly limited and must always be guided by scientific principles; the prescription of hormones empirically or with a faulty technique merely brings organotherapy into disrepute. Moreover, the therapeutic application of endocrinology is still handicapped by the expense of most preparations and by the lack of accurate knowledge regarding the absorption, utilization, inactivation, destruction, and excretion of the hormones in question.

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SCIENTIFIC RESEARCH IN INDUSTRY A YEAR'S WORK

The Advisory Council of the Department of Scientific and Industrial Research, of which Lord Rutherford is chairman, directs attention in the Department's annual report (Cmd. 5350, H.M. Stationery Office, 3s.) to important developments in the outlook of industry in this country. The last five years have witnessed "the fruition of the policy adopted by several large industrial undertakings of setting well-balanced teams of research workers, including chemists, physicians, engineers, and, where necessary, biologists, to solve a particular problem to develop a new product." The future, the report continues, no longer lies with industries content to make sporadic advances at the call of the brilliant individualist; co-operation, team work, and an extensive organization on the technical side are essential for success. For this reason the Department attaches great importance to the development of the co-operative research associations formed under the scheme launched in the early days of its existence.

Savings in the Milk Industry

Valuable work is being done by the Department with the co-operation of the Milk Marketing Board on the purification of waste waters and effluents from milk depots, creameries, and condensed milk factories. Two different methods have been worked out and shown to be successful on a large scale, by which the polluting character of milk washings can be reduced by 99 to 97 per cent. respectively. Investigations have also drawn attention to the losses of milk, cream, whey, etc., carried away in the waste waters. It has been shown that the waste from this cause can be reduced by nearly three million gallons a year. At the low wholesale price of 5d. a gallon for milk for manufacturing purposes this means a saving of about £50,000 a year to the industry. Five per cent. of the total quantities of by-products—whey, skimmed milk, etc.—is frequently lost at present in the waste waters. This loss can be reduced to about 2 per cent. The suggestions put forward for reducing these wastes have already been adopted at several factories.

Storage of Food

At the Low Temperature Station, Cambridge, the effect of radiation from radio-active substances in destroying bacteria is being studied in connexion with the storage of meat. Methods of storing eggs in different concentrations of carbon dioxide are being tried out on a large scale: a high concentration of, say, 60 per cent. prevents attack by mould and gives an excellent yolk but a very fluid white. Experiments have been made on the "gas storage" of pears. British pears have been stored in refrigerated chambers with the atmosphere adjusted to contain the correct amount of CO₂ for long periods, extending well into the summer. When removed from the store the flavour, texture, and appearance of the pears were entirely satisfactory. Excellent results under commercial conditions have been obtained by improved methods for the preservation of peas by freezing. Quick cooling and freezing following blanching in hot water are essential, and the colour and flavour of the peas are improved by the addition of just