THE USE OF OESTROGENS IN OBSTETRICS AND GYNAECOLOGY

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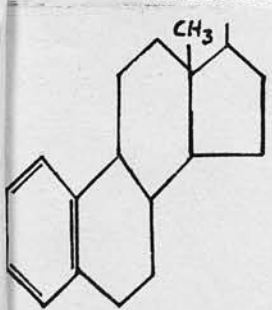
The term oestrogen is applied to substances which are characterised by a capacity to restore oestrus or heat in the castrate female animal.

The pioneer work of Allen and Doisy (1923), is a landmark in the development of sex endocrinology. By using the vaginal smear which Stockard and Papanicolaou (1917) had shown to undergo definite and constant variations in relation to the separate phases of the oestrus cycle, they demonstrated that a substance could be extracted from the ovary which, when injected into castrate rodents, was active in bringing on heat. No progress was made in the isolation of this substance until it was found that large quantities were excreted in the urine of pregnant animals (Ascheim and Zondek, 1927). The crystallisation of the substance (Butendandt, 1929; Doisy et al., 1929: Marrian, 1929) was early followed by demonstration of its relation to the sterols - one of the most important biochemical groups in normal and abnormal metabolism - and eventually five naturally occurring oestrogens were isolated from the ovary, pregnancy urine and the placenta, all with an identical basic formula (1) and a similar qualitative action.



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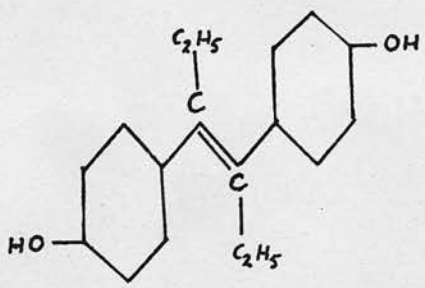

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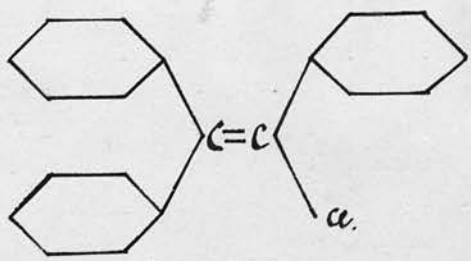

3.

Of these three are used clinically, viz. Oestradiol (dihydroxyoestrin), Oestrone (ketohydroxyoestrin) and Oestriol (trihydroxyoestrin). That in most common usage to-day is the esterified form of oestradiol known as oestradiol benzoate.

STANDARDISATION.

Until 1935, standardisation was entirely by biological tests, and, as the criteria adopted by each worker varied, it was impossible to correlate results from different preparations and complete chaos reigned. The Committee on Hormones of the League of Nations Permanent Health Commission laid down as the International Unit for Oestrone the activity of 0.1γ (= .0001mg.) of a standard preparation, and later fixed the International Benzoate Unit (I. B. U.) as the activity of 0.1γ of a standard preparation of oestradiol benzoate. By relating the standard to a definite weight of a chemically pure substance the Committee placed Oestrogens on a similar footing to many drugs in the Pharmacopeia, and it is therefore only fitting that oestrogens should be prescribed in milligrams, and not in astronomical numbers of biological units.

SYNTHETIC OESTROGENS.

It was thought until recently that the cyclo-penteno-phenanthrene nucleus was an essential part of any oestrogenic substance. Workers in London and Cambridge (Dodds and Lawson, 1936: Dodds et al., 1938 /

1938 a and b) have however succeeded in synthesizing a surprisingly simple series of compounds which culminated in the production of 4:4' dihydroxy α-β diethylstilbene (stilboestrol) (2), and its derivative dihydrostilboestrol (Hexoestrol). Workers in Edinburgh have developed another synthetic compound, triphenylchlorethylene (3) (Robson and Schönberg, 1937). These synthetic compounds have been shown to have an oestrogenic action similar to the naturally occurring oestrogens (Dodds et al., 1938 b: Robson, 1938) and to be highly active orally. It is possible that they are products of the metabolism of oestradiol and have an initial immunity to break-down by the liver. (Shorr et al., 1939).

ADMINISTRATION.

All oestrogenic substances may be given orally, by injection, and locally through mucous membranes. The natural oestrogens are also effective percutaneously provided an organic solvent such as alcohol or benzol is used (Zondek, B., 1938). On oral administration the synthetic oestrogens are all highly active, whereas the ratio of potency by mouth and by injection of pure natural oestrogen is 1:500 (Inhoffen et al., 1938). There is little difference in the duration of action by mouth of the same large dose of oestradiol, oestradiol benzoate, stilboestrol and triphenylchlorethylene (Robson, Schönberg and Fahim, 1938). By injection, speed and duration of action /

action depend upon the method employed. Short and concentrated action may be obtained by giving a large number of small doses of the natural hormone in aqueous solution. The substance in this case is rapidly absorbed and rapidly broken down by the body. Slower and more prolonged action results from injection of the oestrogen in an oily solution, and this can be enhanced by injecting the esterified substance, e.g. oestradiol benzoate. Triphenylchlorethylene is characterised by a singularly prolonged action when injected in an oily solution - in animals a demonstrable effect is present for nearly 20 weeks (Robson, Schönberg and Fahim, 1938), and in man effects have been seen 6 - 9 weeks after two subcutaneous injections at weekly intervals of 250mg. (Macpherson and Robertson, 1939).

It is apparent that the absolute activities of the natural and synthetic oestrogens are dependent upon threshold activity, duration of action and intensity of action (Miescher, Scholz and Tschopp, 1938). Consequently, accurate comparison between them for clinical usage is difficult. Oestradiol benzoate by injection and stilboestrol orally have a corresponding threshold activity and approximately the same duration of action, i e. dosage will be similar and will amount to a very few milligrams. The threshold activity of triphenylchlorethylene is approximately 1/10,000 that of oestradiol, but its action is so concentrated and, by injection, so much more prolonged (Robson, 1938) that dosage is not higher in proportion to the difference in threshold /

threshold activity.

Three points must be borne in mind for successful oestrogenic therapy. Firstly, the substances do not act instantaneously. Even with frequent small injections of aqueous solution, maximal action does not occur for about 24 - 48 hours, and after administration of an oily solution or by mouth, the latent period is longer than this, probably at least three days. Consequently, where oestrogens are given to make up a deficiency or as an antagonist to another hormone, full clinical effects should not be expected under these times. Secondly, prolonged and continuous treatment will result not only in deleterious local effects in the uterus and breasts, but to some extent in pituitary and hence in ovarian inhibition. Where prolonged treatment is contemplated, therefore, it should be arranged "in courses", so that there is an interval during which the organism is subjected to a progressively decreasing quantity of circulating oestrogen, a condition similar to the normal cyclical activity of the follicular hormone. Thirdly, the effects of oestrogen administration are transient, and when the circulating blood oestrin falls below the level of endometrial stimulation, bleeding will occur from the uterus. This oestrin withdrawal bleeding appears 5 - 12 days after the cessation or reduction of treatment and can be controlled by further oestrogen administration.

PHYSIOLOGY /

PHYSIOLOGY.

The natural ovarian follicular secretion is responsible for the growth and adult development of the secondary sexual apparatus - uterus, vagina and breasts. It is essential for proliferation of the endometrium during the first part of the menstrual cycle and, in its absence, progesterone is unable to induce the secretory changes characteristic of the progestational phase of the cycle. It increases the vascularity and hence the size, and the metabolism of the uterus. Under its influence, both the spontaneous activity and the reactivity of the muscle to the oxytocic principle of the posterior pituitary lobe are increased. It causes cornification of the vagina and increases the mucous secretion from the cervix. In the breast, it is concerned in the growth of the ductular system and acts with the luteal hormone in stimulating alveolar development (Nelson, 1936). It appears to be antagonistic to, or at any rate to have an inhibitory effect upon the gonadotrophic (Rowlands and Sharpey Schäfer, 1940), and lactogenic principles of the anterior pituitary (Nelson, 1936).

OVARIAN DEFICIENCY.

Clinical usage is rationally determined by the deficiency of some or any of these functions. Diminished ovarian secretion commonly leads to the symptoms included under the term "menopausal". In the menopausal syndrome, disturbances of the autonomic nervous system /

system, of such a character as to suggest a sympathetic irritability and a parasympathetic depression (Donald, 1937), are outstanding - hot flushes, sweatings, palpitations, tachycardia, coldness of the extremities, migrainous headaches, true menopausal hypertension, urinary sphincteric irritability, obesity - but other neurogenic symptoms of more uncertain origin also occur, for example insomnia, vertigo, emotional instability amounting even to a paranoid psychosis (Strachan and Skottowe, 1933). Amenorrhoea, oligomenorrhoea, frigidity, and varying degrees of atrophy or of failure of development of the secondary sex organs are the characteristic genital symptoms of ovarian deficiency, and certain general effects may also occur - menopausal arthritis, especially of the metacarpal joints (Hanne, 1937) fibrositis, hyperthyroidism, allergic manifestations arising apparently de novo (Donald, 1937), hirsutism, possibly a suprarenal cortical phenomenon (Zondek, H.,1935), and other skin changes. In relation to the syndrome described as menopausal, it is important to notice that a symptomless cessation of the menses ("menopause") may be followed some years later by "menopausal" (true "climacteric") symptoms (Bishop, 1937 b: Donald, 1938).

PRINCIPLES of TREATMENT of MENOPAUSAL SYNDROME.

After the cessation of the menses, oestrogenic substances can frequently be recovered from the blood even where the menopause follows surgical castration. The presence or absence of this oestrogen /

oestrogen bears no relation to the severity of symptoms (Fluhmann and Murphy, 1939). From the same patients, gonadotrophic hormone can almost invariably be recovered in excessive quantities, but, while the amount of the excess appeared at first to be associated with the degree of the symptoms, it has since been shown that this excess may persist for the remainder of life, long after the symptoms have disappeared (Heller and Heller, 1939). It follows that the symptoms are not due to the excessive secretion of gonadotrophic hormone per se, but are dependent upon a temporary imbalance of the anterior pituitary, cortical suprarenal and follicular secretions. Oestrogenic therapy, by antagonising the gonadotrophic secretion, temporarily restores the endocrine balance and allows the patient gradually to become accustomed to a new level of endocrine activity (Bishop, 1937 b). It is apparent, therefore, that prolonged treatment will be essential; that as the adult organism is accustomed to cyclical variations in the amount of circulating oestrin and is liable to injury from continuous administration, treatment should be arranged in "courses" of about three weeks duration; that dosage should be worked up from a small amount to a point where symptoms are completely controlled, and should then be gradually reduced over a considerable time. A year may be necessary to obtain permanent relief, or small doses may have to be continued indefinitely; and the dosage in different cases will vary so much that a method of controlling the effect of treatment is /

is essential.

Two satisfactory methods of control are available - a subjective record by the patient herself of all flushings experienced over a set period during each course of treatment; and an objective record in the vaginal smear. Briefly, the smear from a vagina under the influence of oestrin consists essentially of flat cornified cells, with pyknotic nuclei, isolated or in small groups, (Papanicolaou, 1933). In the menopausal state, these cells, if present at all, are irregularly folded, indefinite in outline and clumped together, and show only slight cornification. Leucocytes and cellular débris are generally abundant, and a few rounded cells with large nuclei from the deeper layers of the vagina may also be present (Papanicolaou and Shorr, 1936). Alteration under oestrogenic treatment from the menopausal to the"oestrus"smear, and maintenance of the smear at or near the oestrus state is the most accurate measure of the efficacy of treatment in the menopausal syndrome.

For such prolonged treatment, oral administration is preferable, and the potency of the synthetic oestrogens by this route makes one or other of them the obvious choice. To exclude purely psychological effects, it is often advisable to begin with a course of inert tablets outwardly similar to the ones which are eventually to be used for treatment. Thereafter, till the symptoms are controlled, courses of increasing intensity are given, firstly to preclude the risk of overdosage /

overdosage and secondly to obviate as far as possible the toxic side actions which may occur with synthetic oestrogens. Dosage must vary with the individual requirements, but a useful sighting shot is 0.5mgm. of stilboestrol or 600-800mgm. of triphenylchlorethylene daily, subsequent alteration in dosage being made according to the response to treatment.

ATROPHIC VULVITIS and VAGINITIS.

The most troublesome to treat of all the menopausal disturbances may be the atrophic conditions of the vagina and vulva, senile vaginitis, kraurosis vulvae and leukoplakia vulvae. Such genital tract atrophy is always associated with severe ovarian failure. Normal ovarian function not only causes cornification of the superficial layers in the vagina, but also leads to the appearance of glycogen in the epithelial cells and a lactic ferment in the vaginal secretion, which causes its acidity and allows the Döderlein's bacillus to flourish and make it even more acid (Dobszay, 1936: Cruickshank and Sharman, 1934) In the presence of certain types of infection, such as gonorrhoea or trichomonas, oestrogenic therapy alone can never restore the normal vaginal smear and flora. Hence, in any vaginitis near the menopause, it is of the utmost importance first to establish the diagnosis of infective or senile. In the latter case, oestrogenic therapy is indicated and again must be controlled by response. Individual requirements vary greatly - one series

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publishes doses varying between 10 and 70mg. per week of oestradiol benzoate subcutaneously, (MacGregor, 1938) another 0.1-5mgm. of stilboestrol daily by mouth (Bishop et al., 1939) and yet a third 400-1,200mgm. of triphenylchlorethylene daily by mouth or 250-750mgm. monthly by injection (Macpherson and Robertson, 1939). If adequate dosage is given early, the response to treatment is striking. Local applications are disappointing, possibly because the vaginal condition is too atrophic to absorb sufficient oestrogenic substance (MacGregor, 1938). Kraurosis vulvae is more resistant to treatment, and energetic therapy must be prolonged after the lesions have healed or recurrence is certain. Leukoplakia vulvae rarely responds entirely to oestrogens as the ovarian deficiency is not, as a rule, the only underlying cause. Supplementary treatment with Vitamin A and hydrochloric acid orally may be helpful, and the urine must always be tested for sugar.

VULVO-VAGINITIS BEFORE PUBERTY.

The neonatal vagina is under the influence of maternal oestrogen for about two weeks post partum and during that time the smear, secretion and flora are all adult in type. Thereafter, until puberty, the secretions are scanty and alkaline (Cruickshank and Sharman, 1934). The rationale of oestrogenic treatment of vulvo-vaginitis in childhood is temporarily to restore the adult bactericidal environment for example by 0.5mg. of oestrone daily by mouth or 0.1mg. oestradiol benzoate /

benzoate daily by injection, plus suitable local cleansing methods, for 3 or 4 weeks (Nabarro and Signy, 1935). Oestrogen has been supplanted in the treatment of pre-pubertal vulvo-vaginitis by the sulphonamides, but it may still form a useful adjunct to sulphonamide therapy, or may replace it entirely where these compounds are not well tolerated.

IN PREGNANCY.

Bearing in mind the experimental effect of oestrogen upon the activity and reactivity of the uterine muscle, many attempts have been made to induce abortion or premature labour by its use. The continuation of normal pregnancy is, however, assured by such a generous inhibitory hormonal balance, both quantitatively and qualitatively, that no success has been obtained in this direction with the natural oestrogens. Nor is this surprising when one compares the enormous quantities of circulating oestrin necessary for the sensitisation of the pregnant uterus to the posterior pituitary hormone at term with the relatively insignificant amount of combined and therefore rather inactive oestrin circulating in the early months (Browne et al., 1939). Even near term, induction of premature labour by oestrogens alone requires large and repeated doses, and even as an adjunct to quinine-pituitary induction, fails to evoke uterine contraction in fully 50% of cases. (Jeffcoate,1939). As a method of induction of labour it is, therefore, not only uncertain /

uncertain, but so slow as frequently to take a week to bring about its effect.

On the other hand, properly used, it has been shown to be effective both as a prophylactic against and a curative for uterine inertia. It should not be used as the first resort in established uterine inertia, even where such obvious causes as pelvic disproportion, malpresentation, local lesions of the uterus and emotional states can be excluded. If, however, after treatment with morphia and other sedatives uterine contractions are not established, or where the uterus remains flaccid after mechanical induction of labour, the injection of oestradiol benzoate in 2mgm. doses hourly for at least 10 injections, or until labour is nearing a successful termination, is reported to have produced excellent results in 50% of cases (Jeffcoate, 1938). Such treatment is expensive, but there is no reason to doubt that oral administration of the synthetic oestrogens in corresponding doses - 1-2mgm. of stilboestrol or 600-800mgm. of triphenylchlorethylene hourly - would have identical results. In any case so treated particular watch must be kept for the possible occurrence of "toxic" reactions (q.v.)

When pregnancy has become abnormal and the hormonal balance disturbed in consequence, better results can be expected from suitable endocrine therapy. In missed abortion, carneous mole

and /

and intra-uterine foetal death, the circulating blood oestrin is considerably reduced (Spielman et al., 1931: Bishop, 1935). The uterine muscle, therefore is not sensitised to oxytocic principles and does not expel its contents. Exhibition of oestrogens in large doses - 4mg. of oestradiol benzoate t.i.d. by injection, or 1,200-1,800mg. of triphenylchlorethylene daily - if necessary, with the addition of quinine-pituitary induction about the sixth day of treatment - is reported to have been successful in causing evacuation of the uterus in 80% of cases (Jeffcoate, 1937). It should be noted that this treatment is useless in incomplete abortion where the residual fragments of placenta or membranes are usually adherent to the uterine wall.

LACTATION.

The oestrogenic hormones are intimately concerned with the physiology of the breasts in two ways. In the absence or in hypofunction of the ovaries, the breasts fail to develop, but normal virginal growth can be stimulated by the exhibition of oestrogens. Broadly speaking, in the human, oestrogen is probably responsible for the growth of the duct system and with progesterone will cause alveolar hyperplasia (Nelson, 1936). This is a possible and simple explanation of the enlargement of the breasts which normally occurs in pregnancy. Thus, oestrogen has, as upon all the secondary sexual apparatus, a direct stimulatory effect /

effect upon the breast. It has already been pointed out, firstly, that at the onset of parturition the quantity of circulating blood oestrin is enormous (Browne et al., 1939); and secondly that oestrin is antagonistic to that factor of the anterior pituitary which is believed to be directly concerned with the initiation and actual maintenance of lactation (Riddle et al., 1935). These two factors prevent the secretion of milk during pregnancy, but post-partum there is such a dramatic drop in the oestrin content of the body that the lactogenic factor can act unopposed upon the breast and secondary organs, causing milk secretion in the former and abetting involution in the latter. On the other hand, experimental stimulation of breast development and lactation in virgin mice by suckling alone, (Selye, 1934; Selye et al., 1934; Selye and McKeown, 1934 a and b), the delayed effect of sympathectomy upon an apparently normal lactation (Cannon and Bright, 1931), and the clinical regression of the breasts when the stimulus of suckling is withdrawn, suggest that, once lactation has been established, nervous factors are involved in the maintenance of the lactogenic hormone secretion. This is further demonstrated clinically in that inhibition of lactation can be brought about by adequate oestrogen administration before or after the appearance of milk in the breasts, but that less oestrogen is required and a quicker inhibition is obtained when the milk is already established by suckling. It is essential that energetic /

To face Page 16.

	First Course.						Second Course.							
			Dosage.				Indication			Method.		Result.		
	Method.	Number.	Total. (mgm).	Single (mgm).	Days Given.	Complete Inhibition.	Secretory Activity.	Painful Nodular Breast.	Infection.	Oral.	Injection.	Satisfactory	Other Treatment Required.	
All Cases.	Oral	7	3,800 — 4,800.	400	4–6	5	-	1	1+	2	-	1	1+	
	Injection.	45	250–300	250–300	1	34	3	6	2ϕ	2	9	9	2ϕ	
	Total.	52				39						10	3	
Administration less than 24 hours Post-Partum.	Oral.	3	4,000	400	4-5	3								
	Injection.	29	250-300	250–300	1	26	1	2	-	2	1	3	-	
	Total.	32				29						3	-	

energetic treatment be given. The organism is accustomed to a heavy concentration of circulating active oestrogen, and no harm can accrue from massive dosage. To this end the synthetic compounds are most suitable, and triphenylchlorethylene appears to be especially well-adapted. Its intensity and duration of action are such that one injection of 250-300mg. given early in the puerperium is sufficient to inhibit any lactational activity or engorgement in 80% of cases. The following table is drawn from cases in which triphenylchlorethylene was used to inhibit lactational activity in Dr. W. F. T. Haultain's wards in the Royal Infirmary, Edinburgh.

CHRONIC MASTITIS.

On the ground, firstly, that the patient is more acutely conscious of the painful nodularity of chronic mastitis in the immediate premenstruum that is when the circulating oestrin, and presumptively the tissue oestrin, is relatively low, and secondly, that in the later months of pregnancy, when the quantity of circulating oestrin is rapidly increasing, the disease tends to decrease /

decrease in severity, the use of oestrogens has been advocated in the treatment of fibro-cystic mastitis. Reported results have so far been inclusive, whether by concentrated cyclical or continuous smaller dosage treatment, but suggest (1) that endocrine treatment is of little value in long-standing cases of fibro-cystic disease; (2) that in young girls with persistent and painful localised nodules, oestrogen administration may afford complete relief; and (3) that the psychological impression of an injection is in many cases as effective a therapeutic force as the most powerful oestrogenic or androgenic substances (Atkins, 1938: Spence, 1939).

AMENORRHOEA.

If the adult female is oöphorectomised and the uterus left in situ, bleeding will occur one to two weeks after operation. Similarly if an oestrogen course of sufficiently high dosage is given to a post-menopausal woman, bleeding will take place 1 - 2 weeks after the last administration. This is known as "Oestrin Withdrawal Bleeding", and occurs when the oestrin level in the blood falls below that necessary for endometrial stimulation i.e. when it is withdrawn from superthreshold level (Bishop, 1937 a). Oestrin is secreted throughout the menstrual cycle, but its proliferative action on the endometrium is limited to the first half of the cycle. In the second half, the hormone of the corpus luteum, for whose action both prestimulation by oestrin and its simultaneous presence are essential (Robson, 1934), not only inhibits the /

the action of oestrin, but, by its own action upon the endometrium, prevents the occurrence of oestrin withdrawal bleeding (Corner, 1939). When therefore towards the end of the second half of the cycle, a synchronous fall in the body content of the two hormones occurs, the endometrium is deprived of all hormonal stimulation and menstruation follows. This is true menstruation from a progestational endometrium. Oestrin withdrawal bleeding occurs from a proliferated endometrium and may occur naturally, the bleeding being superficially indistinguishable from normal menstruation (Robson, 1937).

Before jumping to the conclusion that a case of amenorrhoea is one of primary sex-endocrine hypofunction, other possible causes must first be excluded, for example anaemia, tuberculosis, change of environment, emotional disturbance, hyperthyroidism, obesity and pituitary disorders generally. Thereafter, amenorrhoea is usually due to a sub-threshold effect of oestrin upon the uterus with resultant hypoplasia of muscle and endometrium (Bishop, 1937 a). Broadly speaking, this may be the result of ovarian hypofunction, either primary, or secondary to hyposecretion of pituitary gonadotrophin, of uterine insensitivity to normal quantities of circulating oestrogen, or to a combination of the two. It is important in the first instance to ensure a uterus of normal size and function, and herein lies the clearest indication for oestrogen therapy in amenorrhoea. High dosage is usually essential - 25-40mg. of oestradiol benzoate in divided doses by /

by injection (Bishop, 1937 a), up to 700mgm. of stilboestrol (Buxton and Engle, 1939) or 10,000-16,000mgm. of triphenylchlorethylene orally (Macpherson and Robertson, 1939), all over a period of a fortnight. If dosage is adequate and the uterus responsive, withdrawal bleeding will occur 6-12 days after treatment is stopped, and, if uterine deficiency is the sole cause of the amenorrhoea, after a few regular courses, rhythmical menstruation may be established. This is more frequent in secondary amenorrhoea, particularly in cases of super-involution, where good results with what is now known to have been relatively weak doses of oestrogenic hormones have been described (Haultain, 1933). In primary amenorrhoea, however, permanent response to oestrogenic therapy alone is rare, and once uterine size and sensitivity are established, ovarian stimulation by gonadotrophins will constitute the second stage of the treatment.

DYSMENORRHOEA.

The place of hormonal therapy in dysmenorrhoea must, on the other hand, be considered to be indefinite. Local causes must first be excluded so far as possible Thereafter three elements remain - nervous, psychological, and endocrine - and the assessment of their individual responsibility is a difficult problem. Broadly speaking, however, there are certain indications for hormonal therapy, based on the assumption that a qualitative imbalance exists between the two ovarian hormones. Where uterine hypoplasia exists, oestrogenic therapy /

therapy is indicated either along similar lines to that suggested for amenorrhoea (Johnstone, 1940), or throughout the cycle if the dosage is considerably reduced (Bishop, 1937 a). "Membranous dysmenorrhoea", generally associated with premenstrual colicy pain, may originate in a relative excess of progesterone, or more probably in an excessive reaction on the part of the endometrium to the dominant luteal hormone in the second half of the cycle. Oestrogenic therapy during the last week of the period, for example three injections of 5mgm. of oestradiol benzoate, stilboestrol 5-10mgm., or triphenylchlorethylene 800-1,200mgm. orally for 4 days, may be effective in counteracting the excessive response by reducing the amount of active progesterone (Johnstone, 1940).

STERILITY.

Sterility is another problem wherein endocrinology has a place, but it is rarely possible to ascribe sterility to one single cause. It is essential to remember that thorough investigation of the genital functions of both parties should precede any attempt at endocrine therapy in the female (Meaker, 1934).

The importance of the ovary in relation to fertility is twofold - firstly, as the source of the ovum, and secondly, as an endocrine organ. That normal menstrual rhythm may continue in the absence of ovulation has been demonstrated many times (Novak, 1934; Jeffcoate, 1935), and where this does occur, the aim of therapy is to stimulate ovulation. Gonadotrophic hormones are usually employed for this purpose /

purpose. but successful treatment has been described by the technique of "Oestrogen-shock" (Clauberg, 1935). It is asserted that a single powerful injection of oestradiol about the twelfth day of the cycle may produce such sudden inhibition and subsequent release of anterior pituitary gonadotrophin that ovulation and luteinisation, and hence the possibility of conception, may occur.

Where there is apparent genital hypoplasia, whether vaginal, uterine or tubal, benefit will, and success may, be obtained by concentrated oestrogenic therapy similar to that for hypoplastic amenorrhoea (Clauberg, 1935). If there is an already established menstrual rhythm, it is essential to avoid heavy oestrogen administration. Excess of circulating oestrogen in the second half of the cycle may so inhibit the action of progesterone that an endometrium suitable for the embedding of the ovum is never attained. Selected amounts, for example 1-5mg. of oestradiol benzoate weekly by injection may actually augment the secretory phase.

If lipiodol insufflation does not demonstrate tubal patency, provided no gross inflammation is or has been present, i.e. where functional occlusion is suspected, treatment with oestrogens may so increase the size and rhythmic contractions that patency may result (Clauberg, 1938; Geist et al., 1938). Oestrogens appear to have a stimulating action on the tubal mucosa at any time in the cycle. This fact suggests that the patency of a salpingostomy or more /

more rapid and normal healing in any conservative operation on the Fallopian tubes may more certainly be expected if oestrogens are given for 48 hours before and for a week after operation (Caffier, 1938).

FRIGIDITY

Sexual frigidity theoretically ought to be amenable to adequate oestrogen administration. Experimentally, however, mating reflexes are the most difficult oestrus phenomena to obtain (Parkes, 1929; Marrian and Parkes, 1930; Hemmingsen, 1933), and in some species cannot be obtained with oestrogenic hormone alone (Dempsey et al., 1936). In the human, therefore, dosage might have to be so large as certainly to produce unpleasant reactions.

"TOXIC" ACTIONS of OESTROGENS.

All the known oestrogenic substances, themselves concerned in maturing the organism, are related chemically to substances more intimately concerned with growth of normal and abnormal tissues, for example, the organisers of the embryo, and the carcinogenic hydrocarbons. It is known that sufficient oestrogen administration in a selected susceptible strain of mice causes first feminisation and then carcinoma formation in the male breast (Lacassagne, 1932, 1933, 1934, 1936, 1938; Gardner et al., 1935). It has been demonstrated (Geschickter, 1939) that administration of sufficient oestrogen by injection or pellet implantation produced mammary carcinoma in 25 out of 86 rats (in whom spontaneous /

spontaneous breast cancer is very rare). This work awaits confirmation, however, for Emge (1939) failed to induce mammary carcinoma in rats with oestrogens. It is known that painful swelling of the breast may occur in post-menopausal patients under treatment with oestrogen (Werner and Collier, 1933). It has been found that the blood oestrogen content of carcinomatous patients of either sex is sometimes raised (Dingemanse et al., 1930). The deduction made by some is that oestrogens are dangerous and potentially carcinogenic in the human. It must be remembered, however, (1) that the mice are treated with porportionate doses which could not long be tolerated by any human, (2) that treatment must be given for a period corresponding approximately to 15 years in the life of man, (3) that these mice are specially bred as a cancer-susceptible strain, (4) that when painted on the skin of mice for long periods, oestrogens do not induce carcinoma as do the common chemical carcinogenic agents, and (5) that, with rare exceptions, it has been impossible to induce carcinoma by the use of oestrogen alone, however large the dose. Some other factor, genetic or chemical, must also be present and its carcinogenic capacity may be increased by the direct stimulus of the oestrogen upon the mammary gland. On these grounds, it is possible that prolonged treatment in a woman susceptible to mammary carcinoma may hasten its clinical appearance, but is extremely unlikely to initiate malignant growth <u>per se</u>.

On /

On the other hand, it has been shown that continuous oestrogen administration for a period of some weeks in the guinea pig will cause uterine and extra-uterine fibrosis and even fibromyomata, which regress after cessation of treatment (Lipshütz and Vargas, 1939). The association of uterine fibromyomata with some degree of cystic degeneration in the ovaries, and their tendency to regress after the menopause, to growth during pregnancy and to rapid involution in the puerperium are well known. The facts are suggestive, and emphasise the necessity of "courses" in any prolonged treatment with oestrogen.

Administration of the synthetic oestrogens may be complicated by unpleasant reactions, among which gastro-intestinal upset predominates. This "toxic" action appears to be considerably more marked with stilboestrol, but the incidence of toxic symptoms and signs varies greatly with different observers, both in human therapy and animal experiment. Loeser (1939) describes degeneration in the liver and enlargement of and haemorrhages into the suprarenals in rats, whereas Morrell (1939) finds no pathological changes. Bishop et al. (1939) and Winterton and MacGregor (1939), using relatively small doses, found a low incidence of toxicity, but American (Shorr et al., 1939) and French (Varangot, 1939) workers with therapeutic doses found that stilboestrol, both orally and by injection, produced toxic symptoms in 80% and 45% respectively, that there was no "safe" level of dosage and that there was no evidence of increasing tolerance if they persisted with /

with treatment.

On the other hand, over periods varying from 1 to 6 months, while reactions were present in 6 cases, significant deviation from normal in tests on blood and urine was found in only 1 out of 17 cases (Buxton and Engle, 1939). With triphenylchlorethylene, the only published series (Macpherson and Robertson, 1939) states that gastro-intestinal symptoms occurred in 5 out of 41 cases, to all of which the drug had been given orally, and that in no case were the symptoms of such severity as to necessitate cessation of treatment. Obviously the extent and importance of the toxic factor has not yet been completely assessed in the use either of stilboestrol, by reason of the extreme diversity in its reported incidence, or of triphenylchlorethylene, where the apparent non-toxicity awaits confirmation.

Bleeding may occur during oestrogen administration if, for some reason, the blood oestrin falls below the threshold of endometrial stimulation. Patients under treatment for climacteric symptoms should always be warned of this possibility. It can be corrected by further oestrogen administration.

Prolonged and continuous therapy, by adversely affecting the pituitary gonadotrophic secretions, depresses ovarian activity (Moore, 1932). This is a factor which must be taken into account in the young, and counsels the advisability of intermittent administration. In the elder patient, continuous treatment may cause tender swelling of the /

the breasts, cystic endometrial hyperplasia, or weakness, headaches and loss of appetite - these latter probably by pituitary inhibition, (Editorial Lancet, 1936; Donald, 1939), or exhaustion (Severinghaus, 1939).

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