attributed to the mildness of the infection. Manson,³ in America, agrees with Paterson's views, and emphasizes the importance of early administration of large doses of antitoxin by the intravenous route.

Topley and Wilson⁴ suggest that the difference between Sherrington's results and the therapeutic results obtained in man may be due to the fact that he used toxin only and not bacilli. In man the effects obtained with antitoxin would appear to depend, not only on whether it can neutralize toxin which has reached the nervous system, but on the neutralization of toxin in the wound before it has become attached. The apparent success of very large doses of antitoxin may perhaps be explained by the neutralization of toxin in the tissues before it has reached the nervous system. In this way large doses of antitoxin, combined with local treatment of the wound, may prevent further absorption of toxin. If this can be done before a lethal dose has reached the nervous system, death may be prevented.

Treatment of active tetanus may therefore be directed along the following lines. It may aim at preventing further production of toxin in the wound by thorough local measures; at neutralizing any further toxin which is formed in the wound in spite of local treatment by giving large doses of antitoxin; at neutralizing toxin which is already fixed to the nervous system by giving large doses of antitoxin (assuming that this is possible from Sherrington's experiments); at neutralizing toxin by non-specific measures, such as the intrathecal injection of carbolic acid, as used by Suvansa⁵; at preventing spasms and pain; and at maintaining strength by general measures.

In a small series of clinical cases such as this it is impossible to say how far antitoxin was of use; still less is it possible to compare the value of the routes used. Ten cases were treated and five recovered. This does not compare with Paterson's results, but it should be remembered that of the five patients who died two were men of 60 and 73, while two others had deep infected wounds of great severity, which prophylactic antitoxin might have saved. The five patients who recovered had doses of antitoxin ranging from 234,000 to 360,000 units, given chiefly by the intravenous and intrathecal routes. In any case of tetanus it is extremely difficult to give a prognosis, and therefore to assess the results of treatment. Large doses of antitoxin, however, did appear to influence the course of the disease favourably in these cases, by lessening the severity and frequency of the spasms. The only disadvantage of such treatment is the expense. The cost of 100,000 units of serum is approximately £4.

SUMMARY

Tetanus is still sufficiently common in some districts to make it worth while re-emphasizing the importance of prophylactic antitoxin, even after trivial wounds.

When the disease has developed the following rules should be observed.

1. Diagnosis should be made and treatment begun as early as possible. Pain and stiffness in the back of the neck and spine may be the earliest symptom. These, associated with slight stiffness of the jaw and rigidity of the abdomen, should suggest tetanus.

2. Local treatment of the wound should be thorough, and should be done at the earliest possible moment.

3. Antitoxin should be given as soon as possible in very large doses, preferably by the intravenous route.

4. Every effort must be made by symptomatic measures to reduce spasms and allay pain. For this purpose avertin may prove of value

5. The strength must be maintained by giving plenty of nourishment. For this to be achieved good nursing is essential. Glucose should be given freely.

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REFERENCES

- ¹ Sherrington, C. S.: *Lancet*, 1917, ii, 964.
- ² Paterson, A. E.: *Med. Journ. of Australia*, 1930, i, 832.
- ³ Manson, M. H.: *Minnesota Med.*, 1931, i, 142.
- ⁴ Topley, W. W. C., and Wilson, G. S.: *The Principles of Bacteriology and Immunity*, London, 1929, ii, 1158.
- ⁵ Suvansa, S.: *Lancet*, 1931, i, 1075.

ENDOCRINE THERAPY IN DYSMENORRHOEA

BY

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The common complaint of dysmenorrhoea has caused a widespread controversy as to its aetiology and treatment. Many types of the disorder have been described in terms which have sometimes tended to confuse the problem. This is exemplified by the presupposition of a condition such as "obstruction" without proof of its existence, or by emphasizing the "congestive" element which is normally present in the premenstrual and menstrual phases. Just as a distinction has been drawn between hyperpiesis and hyperpiesia, we prefer to speak of dysmenorrhoea as a symptom accompanying some recognized primary condition such as cervicitis or salpingitis, and dysmenorrhoea as an entity in the absence of any detectable disease. For the symptom dysmenorrhoea, the term "menorralgia" has been suggested, and if it could gain wide acceptance it would have much to commend it. Our special concern here is with the severe cases of dysmenorrhoea, sometimes called primary, idiopathic, essential, or intrinsic, which seek hospital treatment. In these the simpler remedies such as mild analgesics, attention to the bowels, and such exercises as those described by Dr. A. Sanderson Clow, must be frequently amplified by more intensive treatment. This falls into two groups: operative procedures and endocrine therapy. Examination of these seemed desirable with a view to throwing light on the nature of that disordered physiological function which becomes prominent as pain, and affording a rationale for ovarian therapy. This preliminary study was therefore undertaken, and forms part of a more extensive investigation on menstrual physiology and pathology.

The clinical picture presented by the patients who come to hospital for relief is of the following kind. They are generally unmarried and nulliparous, and the onset of the complaint usually dates from two to three years after the menarche, though in a few cases it coincides with the first menstruation. Apart from the critical time the patient feels well, but some days or hours before the onset of each period, strong cramp-like or colicky pains commence in the mid-line of the lower abdomen, and less frequently in the low lumbar or sacral regions. The pain reaches its greatest intensity at or just after the beginning of the flow, and then commonly subsides. It may, however, occasionally continue throughout, and even for one or two days after the period. The pain is often so severe as to necessitate the patient going to bed, and is accompanied by greater or lesser degrees of malaise, anorexia, vomiting, headache, and sometimes manifestations of reduced vasomotor control as evinced by cold hands and feet, etc. The periodicity may be either regular or slightly

irregular, with a tendency for the intermenstruum to be short and the loss to be rather excessive. Thirty-one of our fifty cases exhibited this characteristic, while only two showed definite oligomenorrhoea. Leucorrhoea frequently occurs prior to the flow, and to a lesser degree after the period.

OPERATIVE MEASURES

Dilatation of the cervix is widely practised for the relief of intractable dysmenorrhoea, and sometimes produces permanent cure, but it is not always successful. Johnstone, collecting the figures of a group of workers, finds that 49.8 per cent., and Holden that 37 per cent., are relieved by this means. The reasons for the procedure and for its partial failure require discussion. For a long time a ruling concept was the "obstructive theory," which held that menstrual pain resulted from an inability of the uterus to rid itself of the blood shed into the lumen owing to a pin-hole os, kinking of the cervical canal through acute antelexion, or stenosis of the cervix. Blair-Bell, in reviewing all his records, was struck by the frequency with which dysmenorrhoea was absent in cases of pin-hole os and conical cervix, and further by the fact that these anomalies were not found in the majority of dysmenorrhoea sufferers. This has been confirmed by numerous other observers, and Eden and Lockyer teach that the condition only contributes to the causation of pain when the uterine muscle is inadequate. This raises an entirely different problem, which will be referred to below. Acute antelexion has been alleged to occlude the cervical canal by the sharp kink between the body and the cervix, but antelexion is the normal resting position of the uterus, and during menstruation the muscular contractions lift the body of the organ into a more perpendicular plane, so straightening the axis of the lumen. Here also the sharp angulation would only seem to interfere when the myometrium is defective.

Stenosis of the cervical canal has often been incriminated as the chief cause of dysmenorrhoea, but, as Blos observes, it is not a constant feature, and dilatation fails to cure at least half of the cases. It is difficult to see why more favourable results are not obtained if the pathology is that of simple stricture, or spasm of the circular muscle, which is certainly overcome by stretching with dilators measuring up to 1.5 cm. in diameter at the tip, as this must cause rupture of some of the fibres. Occasionally deliberate splitting of the circular fibres has been recommended, but apparently with no more favourable results. It has been argued that the effect of dilatation is to stimulate a hypoplastic uterus to grow, though how this can occur is not stated. Moreover, such a result could scarcely be obtained at once, and as immediate relief is undoubtedly given in some instances, this explanation is inadequate. The fact that pregnancy is almost always followed by relief has no necessary bearing on artificial stretching of the cervix, as the changes in the pregnant uterus are so profound that many other factors might be operative. The explanation of cure by dilatation is not clear, but in view of other considerations dealt with below it may be suggested tentatively that it is possibly due to rupturing nerve fibres in the cervix.

CAUSATION OF PAIN IN DYSMENORRHOEA

Before considering endocrine therapy it will be well to examine the pain mechanism as a whole. An ovarian origin was frequently postulated by the older authorities, but now this is not believed to have any significance in dysmenorrhoea. True ovarian pain differs in character from ordinary menstrual pain, and apart from sharing in the general pelvic congestion every month there seems no obvious reason for pain to arise in this organ at the

menses. The pain can be explained completely by reference to the uterus, for it is comparable in all respects to that arising in other unstriped muscle contracting with irregular, unrelated waves, or against an excessive resistance. As in such parallel conditions the area of reference is not sharply demarcated, although the main site may be stated definitely enough, and the description given by the patients of the quality of the pain commonly employs the same terms as for colic and the like. It may now be seen that the actual pain is explicable on the basis of a defect in, or interference with, the neuro-muscular mechanism of the uterus, as, for example, by the presence of an abnormal resistance. The neuro-muscular complex can be examined at three main points: the central or cerebral, the ganglia, and the myometrium. With regard to the first of these one must remember the possibility of truly functional dysmenorrhoea due to definite psychological disturbance. Such cases occur, and their treatment is more a psychiatric than a gynaecological problem (though it should be remembered that suggestion may augment the results of ordinary therapeutic measures). A full consideration of this aspect would, however, involve too wide a digression. Stolper has advanced the suggestion that normally painless contractions, by surmounting the threshold of sensation, might be perceived as painful when the organs are excessively congested. This may possibly occur, and if so, it may follow various hypersensitive states of the nervous system.

INTERDEPENDENCE OF CERVICAL GANGLIA AND OVARIAN SECRETION

The uterine nerves pass through portions of Frankenhäuser's plexus, the ganglia cervicalia uteri, which lie one on each side of the cervix. At first sight these are exactly comparable to other pelvic autonomic ganglia, but it has been shown by Blotvogel and Poll, and confirmed by Kennedy, that they possess the unusual feature of being under the control of the ovarian autacoids. This is shown by the fact that oöphorectomy very rapidly produces degenerative changes in the ganglion, before, in fact, any histological change is demonstrable in the uterus. For a description of the cytology the original papers should be consulted.

It must suffice here to say that the changes are of the reversible degeneration type similar to those exhibited in early intoxications. The Nissl granules of the ganglion cells are lysed, and the cells shrink, while the number of chromaffin cells always associated with the ganglion diminishes markedly. Restitution of the original picture can be obtained by the injection of oestrin, and maintained by repetition of its administration. This phenomenon caused emphasis to be laid on the ganglion as the possible key to the position. If the ganglion is pathological it is reasonable to suppose that the uterus will show the effect of this either by non-rhythmical contractions or disturbed polarity, or, if the trophic impulses are interfered with sufficiently, by becoming hypoplastic. Oöphorectomy does produce uterine atrophy by removing the endocrine influence of the ovary, but it first produces degeneration in the ganglion. It is not then unreasonable to suppose that a perversion of the ovarian autacoid would adversely affect the ganglion and hence the uterus. Further evidence of the importance of the ganglion is afforded by cases of cervicitis. In these a common feature is that moving the cervix elicits pain, which is frequently described by the patient as identical to that suffered at the periods. Further, this is often more severe on one side than the other. After treatment of the infected cervix by cauterization this pain is frequently relieved, and so too is the dysmenorrhoea which is commonly present. The manner in which this relief is brought about will be readily con-

ceivable when it is remembered how difficult the lymphatic drainage of the cervix is. The ganglion is surrounded by a lymphatic channel, and must surely suffer when the lymph is heavily laden with toxic products; when, however, cauterization permits of free drainage, then the irritating substances are removed, and the ganglion can be restored to normal function.

Blos has used alcohol injection of the ganglion with very marked benefit in intractable cases of dysmenorrhoea, on the analogy of the treatment of trigeminal neuralgia. In a private communication this author informs us that he has extended his series to over 100 cases with continued success. He also found that by injecting one ganglion only the pain disappeared from that side, but remained *in statu quo* on the other. This probably indicates that the afferent painful stimuli are blocked at the ganglion; if the contractions remain painful in character they are not perceived as such on the operated side. This method of treatment, especially if it is bilaterally applied, might also regularize the contractions of the uterus, and it is believed that this probably occurs, for the relief obtained is not always immediate, and is sometimes not complete till after the third period following the injection.

We then come to the muscle itself. It has already been seen that a tentative explanation is available for the occurrence of irregular contractions in an otherwise normal organ. Next the question of hypoplasia must be considered. It is obvious that in the underdeveloped, and in the coehleate, uterus the contractile power may be insufficient to rid the organ of the menstrual discharges readily, and this would account for the premenstrual pain and the relief which follows establishment of the flow. The smaller organ, containing relatively more connective tissue, would also tend to suffer in a greater degree from congestion. Hypoplasia forms part of the wider problem of gonadal insufficiency, and this admittedly arises from a legion of causes, from dietary to debilitating disease. On general biological grounds one might expect that the ovary would be more readily affected by any adverse influences than the uterus, owing to its more delicate and complex structure. Furthermore, the ovary admittedly controls and regulates the uterus, and it is here the error should be sought first. It is unlikely that treatment (such as diathermy) directed primarily at the uterus will achieve permanent results if the ovarian "motor" is not set running. The endocrine balance can often be restored by attention to various general unhealthy states, but it is rational to aid and hasten this by the exhibition of active autacoid preparations. Oestrin or theelin produces growth of the uterus experimentally in animals, and we believe it is also effective in the same way in woman, and that its administration for this end is reasonable.

RESULTS OF ENDOCRINE TREATMENT

In the treatment of intractable dysmenorrhoea we have used oestrin for three main reasons: (1) its demonstrated effect on cells of the ganglion cervicalia uteri; (2) its growth-promoting power on the genital tract; and (3) its influence in counteracting excessive haemorrhage. The last of these reasons has not been discussed in detail here as it will be the subject of a later paper. The preparations used have been chiefly tablets and ampoules of sistomensin "ciba" (Clayton) and in addition, progynon (Schering), ovacoids and ampacoids (Reed and Carnrick), and theelin (Parke Davis). Sistomensin for injection is made up in an oily solution, which has the advantage over aqueous solutions in that it affords slower absorption, and thus greater approximation to physiological conditions. On the other hand, oily preparations require to be injected intramuscularly into the buttock, as in the arm the masses

may be painful and may even be obvious as knots. In the gluteal region the injections occasion no pain if given deep into the upper and outer quadrant and well massaged. For a few cases specially prepared gelatin pessaries of sistomensin for administration by the vaginal route were used instead of injection, Pratt and Smeltzer having shown that oestrin is absorbed from mucous surfaces, a fact which we confirmed with these pessaries by animal tests. These gave results similar to those obtained by injection. To maintain as regular a supply of oestrin to the body as possible, injections are supplemented by tablets by the mouth. In a few cases distance from the clinic or exigencies of supply have forced us to use tablets only, and in these benefit has been observed, but never to such an extent as occurs when parenteral methods have also been employed.

The course of treatment now adopted is designed to supply an extra quantity of oestrin from about the period of ovulation onwards, and consists of four injections of one ampoule of the commercial preparation employed, spread over the fourteen days prior to the expected start of the next period. It is not suggested that this is the best possible spacing of doses, though so far this course has given the most satisfactory results, and further experiments are being tried at present. If the pain customarily continues well after the onset of the flow an injection may be given on the first or second day of the period, but as a rule this is not necessary. The tablets are continued till the pain ceases. This is repeated for at least three months, even if no improvement ensues. The course of treatment appears in some cases to lengthen the intermenstruum, even if the cycle is of the regular twenty-eight-day type, and it is well to warn the patient at the start that the appearance of her next period may possibly be a couple of days late.

The results are as follows: completely cured 10; improved 30 (very much improved 11, relieved 15, slightly improved 4); no improvement 10; total 50. Of those cases in the first category five showed a dramatic quality in the relief obtained from more than usually severe symptoms, and all have been observed from at least six months to two years from the cessation of treatment. Certain other fortunate sequelae have been observed in many of the cases—namely, effects on general health, appetite, weight, and euphoria. The look of the patient improves in that subtle way so familiar to the physician, but so defiant of description, and the patients frequently refer spontaneously to a greater feeling of well-being and of freedom from tiredness.

SUMMARY

The pain mechanism of dysmenorrhoea has been discussed and an explanation offered which emphasizes the roles of endocrine dysfunction and of uterine contraction, and refers to the cervical ganglion of the uterus. It is suggested that the administration of oestrin in dysmenorrhoea is rational. Methods and results are presented.

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BIBLIOGRAPHY

- Blair-Bell: *Journ. Obstet. and Gynaecol.*, 1923, xxx, 119.
 Blos: *Münch. med. Woch.*, July, 1929, 1173.
 Blotevogel: *Zeit. f. mikros. Anat.*, 1927, x; *Zeit. f. mikros. Anat. Forschung*, 1928, xiii, 625.
 Blotevogel and Poll: *Med. Klin.*, 1927, xxxix.
 Clow: *British Medical Journal*, January 2nd, 1932, p. 4.
 Eden and Lockyer: *Gynaecology*, London, 1916.
 Holden: *Amer. Med.*, 1905, x, 776.
 Johnstone: *Journ. Obstet. and Gynaecol.*, 1923, xxx, 226.
 Kennedy: *Edin. Med. Journ.*, May, 1929.
 Pratt and Smeltzer: *Endocrinology*, 1929, xiii, 320.
 Stolper: *Wien. med. Woch.*, 1904, Nos. 18-21.