Secondary syphilis may present as pyrexia of unknown origin, the fever being usually low-grade; it may be intermittent, continuous, or remittent. Sometimes the patient complains of sore throat—for which it is only too likely that penicillin will be prescribed in dosage inadequate to cure the disease. Headache, malaise, loss of weight, hoarseness, alopecia, aching pain in long bones, muscles, or joints: any one of these may present as a single symptom or in any combination. Exceptionally the presentation may be with jaundice,[2] anterior uveitis, or choroidoretinitis, or various nerve palsies. The patient may be aware of a non-irritant rash on chest and abdomen, which may be pink rather than dull-red in the early stages, or of non-tender swellings of lymphatic nodes. If for some reason penicillin is given it may be followed within hours by a Jarisch-Herxheimer reaction with increased fever, exacerbation of symptoms, and perhaps the appearance of hitherto absent signs of the disease. Such an occurrence should always give rise to suspicion.

Once the possibility of syphilis is suspected the diagnosis should not be difficult. It is best clinched by finding the causative organism, which may be present in a previously undetected primary lesion and in other surface lesions, especially moist papules and mucous patches. Serological tests are always positive. The importance of making a correct diagnosis is clear enough. Failure may result in disaster for the patient and his family, and the infection may spread widely and inconspicuously among promiscuous people—syphilis is common among practising male homosexuals. Treatment is relatively short and straightforward and the results are excellent; but the physician should be alive to his responsibility for contact tracing, which, after accurate diagnosis and treatment, is the best method of containing the spread of this insidious disease.

[1] Stokes, J. H., Beerman, H., and Ingraham, N. R., Jr., *Modern Clinical Syphilology*, 3rd edn. Philadelphia, W. B. Saunders, 1944.
[2] *British Medical Journal*, 1975, **1**, 112.

Endocrine Treatment in Hirsutism

Idiopathic hirsutism is a disfiguring complaint in women. It may have profound psychological and social consequences, so any effective treatment is welcome. If the excess hair is relatively sparse but troublesome through being coarse electrolysis may be effective, though it is time-consuming and expensive and may lead to scarring of the hair follicles. Other local measures include abrasive pads and depilatory creams; many women find shaving objectionable as it is usually identified with the male and in those with a severe problem provides only a transient and partial solution.

If successful, a therapeutic attack based on endocrine principles would, therefore, have much to offer. In recent years there have been two main lines of approach. The first of these has been the use of corticosteroids, since excess adrenal androgen may be responsible for some cases of hirsutism. In these circumstances a small dose of dexamethasone, say 0·5 mg at night and 0·25 mg in the morning, is given.[1] In theory this should induce enough partial adrenal suppression to reduce the secretion of adrenal androgens but not enough to cause a harmful adrenal atrophy; but this and other potential side-effects make the physician wary of prescribing corticosteroids.

The oral contraceptive pill has also been used to treat hirsutism. The rationale is complex. The ovary may be the source of androgen in some patients with idiopathic hirsutism, and the progestogen inhibits luteinizing hormone and therefore ovarian androgen production and also increases the metabolism of testosterone.[2] The oestrogen component opposes the peripheral action of testosterone and has an important action in increasing the capacity of the plasma globulin to bind sex hormone, resulting in a diminution of the free, physiologically active fraction of circulating testosterone.[3] Sometimes it may be helpful to give both glucocorticoid and oral contraceptive together.

An alternative is to give an antiandrogen, cyproterone acetate. This substance, used sporadically for a number of years, has been recently reassessed.[4] It inhibits hair growth by a direct effect on androgen receptors in the hair follicle as well as by an additional progestational action on testosterone metabolism. Cyproterone acetate has not, however, found general favour because of the fear that a male fetus born to a woman on this treatment could well be feminized, and the long-term effects of this drug are in any case not known.

The results of hormonal treatment for idiopathic hirsutism are notoriously difficult to evaluate objectively, and the responses may take up to a year to appear. Many of the reports are anecdotal. But attempts to make a scientific judgement on the basis of rate of hair growth[4 5] indicate that an endocrine approach to idiopathic hirsutism may offer some hope for a difficult and distressing condition.

[1] Ettinger, B., *et al.*, *American Journal of Medicine*, 1973, **54**, 195.
[2] Gordon, G. C., *et al.*, *Journal of Clinical Endocrinology and Metabolism* 1972, **35**, 444.
[3] Vermeulen, A., *et al.*, *Journal of Clinical Endocrinology and Metabolism*, 1969, **29**, 1470.
[4] Barnes, E. W., *et al.*, *Clinical Endocrinology*, 1975, **4**, 65.
[5] Casey, J. H., *et al.*, *Journal of Clinical Endocrinology and Metabolism*, 1966, **26**, 1370.

A New Line on Dysmenorrhoea

In 1970 the *Index Medicus* listed 17 entries under the heading of dysmenorrhoea; in 1974 there were eight. This might mean that there has been a worldwide decline in the incidence of the condition, but more likely the fall off in publications reflects a waning interest. There has just been nothing new to say.

Treatment should be dictated by cause. When the cause of dysmenorrhoea is mechanical—endometriosis and fibroids are cases in point—the treatment, if not easy, is straightforward. But such secondary forms of dysmenorrhoea are a small proportion of the cases which present in practice. Most often no overt cause for the dysmenorrhoea can be found. In this more common, primary dysmenorrhoea one is left with an unhappy conglomerate of somewhat speculative possibilities. Psychogenic factors, uterine hypoplasia, and cervical spasm have all been invoked. The fact that anovulatory cycles result in painless bleeding and that dysmenorrhoea starts only when regular ovulatory cycles have been established has led to the suggestion that an endocrine factor is implicated. The evidence about the nature of this endocrine factor is somewhat contradictory. The association with ovulatory cycles suggests that progesterone secretion may be relevant. When ovulation is suppressed with oral contraceptives the bleeding often becomes painless, but in suppressing ovulation potent synthetic progestogens are

substituted for the progesterone from the corpus luteum. Nor can the beneficial effect be entirely due to suppression of ovulation: treatment with retroprogesterone, which does not suppress ovulation, often controls dysmenorrhoea.

A recurrent theme in writings on dysmenorrhoea has been the belief that the pain is caused by irregular or excessive uterine contractions. Indeed this is implied in the term "spasmodic dysmenorrhoea" often used to distinguish primary dysmenorrhoea from pain secondary to mechanical causes such as endometriosis. Recordings of the uterine contractions during menstruation in women with dysmenorrhoea show that they have a raised uterine tonicity with some irregularity of the contraction wave.[1]

It is investigations into uterine contractility which have led to a promising new development in the therapy of dysmenorrhoea. For some time prostaglandins have been recognized as one of the natural agents which can cause contractions of the myometrium; indeed part of the early work which led eventually to the isolation of prostaglandins was the discovery of a smooth muscle stimulant in menstrual fluid.[2] Though assays done on peripheral blood have failed to show an increase of prostaglandin $F_{2\alpha}$ in women with dysmenorrhoea,[3] there remains a strong possibility that there is an excessive local concentration of prostaglandin in the myometrium, particularly as the endometrium has now been identified as a major site of prostaglandin synthesis.

It is a short step from the hypothesis that dysmenorrhoea can be caused by uterine contractions due to release of prostaglandin to treatment of the condition by inhibition of prostaglandin synthesis—a step which has now been successfully taken by investigators in Israel.[4] But first there intervened a remarkable piece of serendipidity. Eight months before the Israeli work appeared, a Danish general practitioner published a letter saying that, while treating a female patient with indomethacin for a quite different indication he found that her usual dysmenorrhoea was much relieved.[5] Intrigued by this he treated five more patients: all responded favourably, and he went on to recommend the treatment—without apparently realising that he was using a potent inhibitor of prostaglandin synthesis. The Israelis did a large-scale, controlled double-blind trial with flufenamic acid, which has the property of not only inhibiting prostaglandin synthesis but of preventing the action of these compounds on smooth muscle. They will properly get the credit if this treatment is found to be successful elsewhere, but when plaudits are handed out, the name of Anker Christensen should not be forgotten.

[1] Filler, W. W., and Hall, W. C., *American Journal of Obstetrics and Gynecology*, 1970, **106**, 104.
[2] Clitheroe, H. J., and Pickles, V. R., *Journal of Physiology*, 1961, **156**, 225.
[3] Wilks, J. W., Wentz, A. C., and Jones, G. S., *Journal of Clinical Endocrinology and Metabolism*, 1973, **37**, 469.
[4] Schwartz, *et al.*, *Obstetrics and Gynecology*, 1974, **44**, 709.
[5] Christensen, A., *Ugeskrift for Laeger*, 1974, **136**, 592.

Dangerous Organisms

Provided he has the necessary scientific knowledge, anyone who so wishes can experiment with typhoid or plague bacilli, smallpox virus, or any other human pathogen. Laboratory work on organisms responsible for some serious animal disease is controlled by the Diseases of Animals Act 1950, but at present there is virtually no statutory control over the safety standards of the 600 laboratories in Britain which keep cultures of organisms capable of causing serious human disease.

Surprisingly, perhaps, there have been very few episodes of disease caused by escape of laboratory pathogens, but in 1973 there was widespread public concern after two deaths caused by an outbreak of smallpox traced to the London School of Hygiene and Tropical Medicine.[1] A working party, with Sir George Godber as chairman, was set up at that time to examine the measures required to control the use of human pathogens in laboratories, and its report was published last week.[2]

Too many laboratories hold dangerous human pathogens, says the report: for example, 322 hold *Salmonella typhi* and 287 *Mycobacterium tuberculosis*; 19 hold smallpox virus, and 13 hold rabies virus. The working party listed about 70 "category A" organisms which it considered especially dangerous to human or animal health, and a further list of "category B" organisms which, though dangerous, are not likely to cause epidemics. It recommends that the total number of laboratories holding these organisms should be reduced by ceasing the practice in any laboratory which cannot show good reason for continuing.

Decisions on the safety and desirability of laboratory work with dangerous pathogens should be taken outside the laboratory concerned, says the report, and it proposes that a Dangerous Pathogens Advisory Group should be set up. This would be a small independent body of experts consisting of individuals whose experience would command the confidence of those working in laboratories. Any laboratory wanting to work with an organism in category A would have to apply to the appropriate Government Department, which would ask the Advisory Group to examine the physical conditions in which the work would be done, the safeguards in use, and the justification of the proposed work. No blanket approvals would be given to laboratories to hold all category A organisms. The report stresses that ". . . general scientific merit or even the probability of a specific contribution to knowledge would not themselves justify automatic acquiescence with a request to use category A pathogens. The risk to the public presented by the pathogens must be balanced against the possible benefits to the public to be derived from work on them."

The report also proposes that a code of practice should be drawn up for the handling of category B organisms by laboratories and that it should be brought to the attention of all staff in such laboratories. Legislation should be used to give the Government powers to register laboratories which alone might hold and use specified organisms, to designate the strains to be controlled, to limit the import of such organisms, and to prohibit their transfer within Britain without specific authority.

Bureaucratic control of laboratory research is never popular, but the case presented by the working party seems overwhelming. Undoubtedly the public have been alarmed by accounts of the potential hazards of virus illnesses such as Lassa fever and Marburg disease, and some regulation of institutions doing research on such dangerous organisms is justified. In its early stages the proposed system of control will be voluntary—the necessary legislation will have to wait its turn in the Parliamentary queue—and this period should give research workers a chance to identify any delays or other drawbacks in time for changes to be made.

[1] *Report of the Committee of Inquiry into the Smallpox Outbreak in London in March and April 1973.* London, H.M.S.O., 1974.
[2] *Report of the Working Party on the Laboratory Use of Dangerous Pathogens (Chairman Sir George Godber).* London, H.M.S.O., 1975.