biopsy; one mother required caesarean hysterectomy at 30 weeks after rupture of the uterus. These data reinforce the already strong case for treating young women with positive smears conservatively whenever possible, now a realistic goal thanks to the advent of colposcopy.⁶ We also have reassuring evidence that colposcopy in experienced hands is a reliable diagnostic tool,⁷ which can reduce the need for diagnostic cone biopsy by 90%.⁸ Under colposcopic control effective and less destructive localised treatment of the cervical lesion can be carried out by electrocoagulation, cryosurgery, or carbon dioxide laser.⁸

In Cardiff from 1965 to 1974, 372 of the 600 women who had a cone biopsy were potentially fertile,⁵ and the incidence of positive smears in young women is likely to increase. One of the most worrying statistics about invasive carcinoma of the cervix is that from 1970 to 1975 the death rate in England and Wales doubled in women under 34 years—at a time when mortality was falling in all other age groups.⁹ The rising death rate in younger women may well be due to changing sexual behaviour and, not surprisingly, there are calls for cytology to be offered to women of all ages.¹⁰⁻¹² In the north east of England positive smears were found in 20 per 1000 women from 25 to 34 years and 5 per 1000 under 25. The incidence of positive smears will depend on the population studied; in a group of girls who had been referred for termination under the age of 16, for example, 7% needed cervical biopsy within 10 years of first referral.¹ The anxiety created by a positive smear in a young woman does not provide a reason for immediate cone biopsy because 60% of the abnormalities found in women under 20 years will resolve without treatment.¹ Investigation and treatment must be tailored to the individual

case, and hence we should give priority to providing colposcopy services throughout the country.

Colposcopy will reduce but not eliminate the need for cone biopsy in women of child-bearing age and patients who conceive after an operation on the cervix should be assessed by the obstetrician as early as possible. The need for cervical suture will depend on the history and the clinical appearances of the cervix, and such a patient must have the closest supervision throughout pregnancy to ensure the maximum safety for both herself and the child.

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Regular Review

Acne vulgaris: pathogenesis and treatment

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Too many doctors still regard acne as an untreatable affliction of adolescence—an attitude reflected in a recent survey that found that only one-third of all patients had ever had adequate treatment.¹ Understanding the treatment of acne requires an appreciation of its pathogenesis, in which there are four major factors.

The most important factor is increased sebum production. The sebaceous glands are under complex endocrine control,² being especially influenced by androgens from the testes and adrenals³; and the severity of the patient's acne is related to the greasiness of his or her skin.⁴ The increased seborrhoea may be due to an increase of circulating androgens, especially of adrenal origin; but many patients show no such abnormality,⁵ which suggests that the abnormality is due to the over-responsiveness of the sebaceous glands.⁶

Secondly, the pilosebaceous ducts are obstructed. These are the ducts through which sebum passes to the surface of the

skin. They are lined with keratin continuous with the adjacent epidermis. Some histological evidence suggests that an inflamed acne lesion is preceded by a non-inflamed lesion.⁷ Clinically, these non-inflamed lesions present as "whiteheads" or "blackheads"; but the underlying mechanism is uncertain. Certain fractions of the sebum may be comedogenic⁸ in experiments on animals but not in man.

The third factor is bacterial colonisation. The two main species of bacteria on skin prone to acne and in the follicular ducts are *Staphylococcus epidermidis* and *Propionibacterium acnes*. There is no simple relation between the numbers of these bacteria and the presence or severity of the acne,^{9 10} so what part do they play? Only a few follicles out of many thousands are affected at any one time. The growth of *P. acnes* and the production of biologically active substances by the bacteria vary in vitro with such physiological variables as oxygen tension and pH.¹¹ Since the microenvironment of the

skin also varies considerably—the pH of blackheads ranges from 4.5 to 6.3—optimal conditions for the growth of *P. acnes* will occur unpredictably.

Fourthly, while the part played by bacteria in creating obstruction is debatable,¹² *P. acnes* can produce substances that stimulate the alternative complement pathway¹³ and exert a chemotactic effect¹⁴—both important events in the conversion of a non-inflamed lesion into an inflammatory one.

The pathogenesis of acne depends, then, on the presence of large sebaceous glands: their products may irritate the lining of the follicular duct and help to induce an obstructed lesion. The ducts contain large numbers of *P. acnes*, which given optimal environmental conditions will produce low-molecular-weight substances that diffuse into the dermis and so provoke inflammation by stimulating chemotaxis and activation of the alternative complement pathway. Thus for the rational treatment of acne the physician should consider methods that reduce sebum production and obstruction of the ducts, modify bacterial inflammation, and lessen the inflammatory response. Most currently prescribed drugs affect bacterial metabolism, influencing ductal obstruction and inflammation.¹⁵ Another approach is to reduce sebum production, the main stimulus to acne; then all other pathogenic factors will diminish.

Treatment of acne according to severity—Patients with mild acne need only topical treatment with a preparation containing either retinoic acid or benzoyl peroxide. Patients with more severe acne require systemic treatment as well. The antibiotics commonly prescribed are tetracycline, erythromycin, and to a lesser extent co-trimoxazole. Patients with moderate acne require one tablet (250 mg) twice daily, but those with severe acne need 1 g of tetracycline or more a day,¹⁶ at least initially. Acne requires long-term treatment, but little guidance is available.¹ At Leeds we recommend treatment for at least six months; patients with severe acne may have the dosage of antibiotics reduced to twice daily at three months. If the patient is responding well we then decrease the dose again at six months to once daily and stop oral treatment at seven months.

On this regimen the mean improvement is 60%. Though the patients continue their topical treatment 40% relapse by the end of a further five months; but since the treatment is safe¹⁷ repeated courses can be given. Some patients respond less well than others; youngsters of 14–17 do particularly badly, no doubt because the natural tendency is for acne to worsen at this age.¹ Such patients should therefore be given a dose of antibiotic larger than the severity of the acne might seem to warrant.

Tetracycline, erythromycin, and co-trimoxazole in doses of one tablet twice daily are bacteriostatic but in larger doses are bacteriocidal. They also modify the inflammation of acne directly by inhibiting chemotaxis.^{18,19} One of the recent advances in treatment is a resurrection of a fact documented in the early 1960s²⁰—tetracycline must be taken half an hour before food and not with milk (or iron)²⁰ since it easily forms an insoluble calcium salt. An advantage of erythromycin is its better gastrointestinal absorption. The more expensive tetracyclines have not yet been shown, in adequately controlled trials, to be better than the cheaper BP brands.²¹ Oral clindamycin is no longer recommended except for total, severe, and unresponsive acne because of the risk of pseudomembranous colitis.²²

Benzoyl peroxide is a bacteriocidal agent available in various lotions and alcoholic gels and in various concentrations.²⁵ Usually the patient should have a 5% concentration to apply once a day and be told to expect a little erythema and scaling;

after one to two weeks it should be applied twice daily. Patients with irritable skin should be given a 2.5% gel. Retinoic acid is available as a 0.025% lotion or gel. Patients may experience initial discomfort and they must be warned of possible erythema and a pustular eruption that occurs in three to four weeks.²⁶ This reaction signals dislodgment of microcomedones and is not an indication to stop the treatment, which is aimed particularly at treating comedones and eventually reduces the development of inflamed lesions.²⁷ One comparative study²⁸ showed that benzoyl peroxide had just as much effect on non-inflamed lesions as retinoic acid and more effect on inflamed lesions; the combined use of retinoic acid in the morning and benzoyl peroxide in the evening may produce an additive effect.

Time-honoured compounds such as sulphur, resorcinol, and salicylic acid should now give way to benzoyl peroxide or retinoic acid.²⁹ Artificial sunlight may produce a feeling of well-being and subsequent tanning, but its alleged benefits in acne are disputed.³⁰

Side effects—Occasionally the antibiotics used in acne produce anorexia and nausea, but these symptoms can be relieved by changing the time when the tablets are taken or by lowering the dosage. About 3% of patients develop troublesome colic, usually well controlled by a five-day course of Lomotil (biphenoxylate hydrochloride 2.5 mg and atropine sulphate 0.025 mg). Vaginal candidiasis may occur but usually responds to conventional measures.¹ Tetracycline is contraindicated in pregnancy, and women of childbearing age should be warned of the potential hazard; tetracycline should also be avoided if renal function is impaired. Rare side effects of antibiotics, in particular tetracycline, are fixed drug eruption,³¹ Gram-negative folliculitis,³² phototoxicity,³³ onycholysis,³⁴ and headaches secondary to benign intracranial hypertension.³⁵

Patients need to be told that topical treatment virtually always produces some erythema and scaling, retinoic acid probably more so than benzoyl peroxide. With continued use these symptoms diminish considerably,³⁶ but altering dose regimens may also help. Benzoyl peroxide occasionally bleaches clothes and the hair, and may cause an allergic contact eczema.

Difficult cases—Despite so-called adequate treatment, up to 20% of patients respond inadequately. Some of these patients may not be complying with treatment and this must be checked. A few (less than 1% of patients) will have a Gram-negative folliculitis³² or have *P. acnes* resistant to the prescribed antibiotics.³⁷ These patients require good microbiological investigations. Though patients who do not respond to conventional treatment should be referred to an interested dermatologist, the general practitioner may reasonably try one more trick (in the absence of any contraindication) and give an oestrogen-dominant oral contraceptive such as Minovular to reduce sebum production.³⁸

When the patient has been referred to the skin department, the dermatologist can check again on whether he or she has been complying with the treatment, confer with the microbiologists, and consider giving larger doses of antibiotics. Other possibilities (which need to be tried for four months initially) include treatment with prednisone 5 mg/day for 28 days (a dose that suppresses adrenal androgens) and ethinyl-oestradiol 50 µg (which suppresses ovarian androgen) for 21 days. This combination reduces sebum production by 50–60% by the end of three months.^{39,40} Alternatively, the dermatologist may wish to prescribe an antiandrogen, such as cyproterone acetate 100 mg for the first 14 days of the cycle plus ethinyl-oestradiol 50 µg for 21 days. This sequential combination will reduce the seborrhoea and help the acne con-

siderably in three-quarters of difficult cases.⁴¹⁻⁴² Topical antiandrogens have mostly given disappointing results.⁴³⁻⁴⁵ Some microbiologists prefer the idea of topical antibiotics, but at present topical tetracycline, erythromycin, and clindamycin are available only from some hospital pharmacies. Such preparations seem effective,⁴⁶ but are not yet commercially available.

Other possibilities in the province of the specialist are acne surgery (externalisation of deep sinuses, cryotherapy of large cysts,⁴⁷ dermabrasion of certain scars) and the judicious use of superficial x-rays.

Present and future—Probably the most exciting development in the treatment of acne is a new derivative of retinoic acid. Retinoic acid given by mouth does not help acne,⁴⁸ but 13-*cis* retinoic acid dramatically reduces sebum production and so may dramatically help acne. Given on a body weight basis,

0.1 mg/kg reduces sebum production by 70%, 0.5 mg/kg by 80%, and 1.0 mg/kg by 90%.⁴⁹ As yet, this drug is not available on prescription anywhere, but four studies are currently being undertaken in the United States and one in Britain. Acne is already, however, a perfectly treatable disease. If the doctor is sufficiently enthusiastic and knowledgeable about it the long-term clinical effects of acne can be prevented. But continuous supervision and explanation is necessary; the doctor must especially emphasise that treatment is safe and must be maintained for at least six months—and bear in mind that early treatment reduces the frequency of permanent damage to the skin.

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