Spotting the onset of puberty – the secret's in the skin

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Alice returned home from her first day at Grammar School in tears. Mum sat beside her and tried to coax out of the sobbing youngster the cause of her immense distress. After a few minutes, Alice shouted, 'I hate you. No one will make friends with me because I've got spots. Why didn't you take me to the doctors when I asked you to?'

The onset of puberty marks the transition from childhood to adulthood, through increasing self-awareness and a turmoil of emotions in which feelings and actions are driven by the rising concentrations of sex hormones derived initially from the adrenal glands and then from the developing gonads. The first signs of physical maturation may not be those we normally associate with puberty, but rather more subtle changes in the skin, which lead to oiliness and spots (Fig. 1).

Spots are amongst every teenager's worst nightmares. Just when physical attractiveness really starts to matter, fate has decreed that many youngsters will find their skin rebelling with a colourful display of volcanic eruptions (Fig. 2). Spots can be big or small, inflamed or non-inflamed, superficial or deep, and have the ability to reduce self esteem to rock bottom. One of us well remembers how a handful of spots severely dented her own self-confidence and the habit of avoiding mirrors lingers to this day!

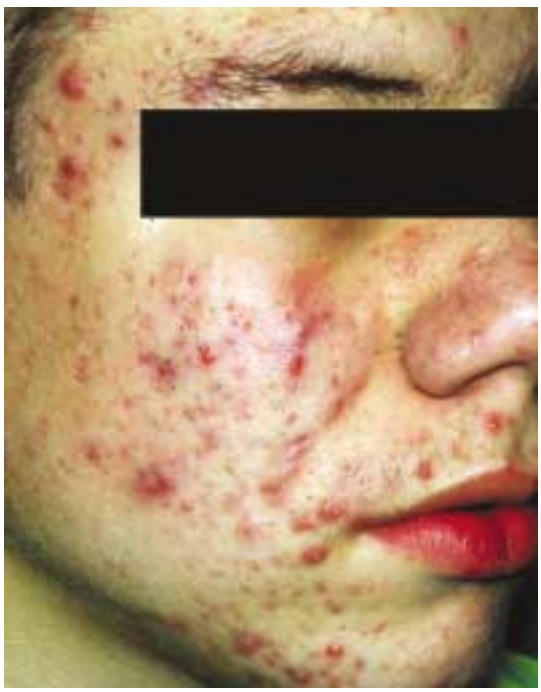
What is acne?

Acne is a multifactorial disease of the sebaceous (grease-producing) glands of the face and upper trunk. Although acne tends to run in families, patterns of inheritance are complex. Under androgenic control, sebum is produced as a holocrine secretion. In humans it has no known function, although there is speculation that it may contain sex steroid-derived pheromones. For reasons that are not well understood, some follicles produce too much sebum. These 'gushers' probably represent acne-prone follicles.

Contrary to popular belief, acne begins not at puberty but before puberty, specifically during the adrenarche when the adrenal glands start producing androgens, including testosterone and dehydroepiandrosterone sulphate (DHEAS) in both sexes. The adrenarche occurs between the ages of 6 and 10. Prior to this, sebum is not produced (except for a brief period immediately after birth). Not all follicles turn on at once. We do not yet know whether those that turn on early are the gushers. A special lipid-absorbent tape, 'Sebutape', applied to the skin can reveal different patterns of sebum production (Fig. 3). If the pattern is homogeneous, the subject is unlikely to be acne-prone.

Patterns become increasingly heterogeneous as acne severity increases – with some follicles producing no or very little sebum. These follicles are functionally blocked by a cornified plug which arises via the hyper-proliferation of the keratinocytes (epidermal cells) lining the duct (infundibulum). This is the second step in the formation of an acne spot. At this stage the lesion is called a comedo. Organ culture studies by Terence Kealey and colleagues at the University of Cambridge indicate that comedogenesis may be triggered by keratinocyte-derived interleukin-1 alpha. Alternatively, high sebum excretion rates have been hypothesized to dilute the essential fatty linoleic acid to deficient levels, which can also initiate hyperkeratosis.

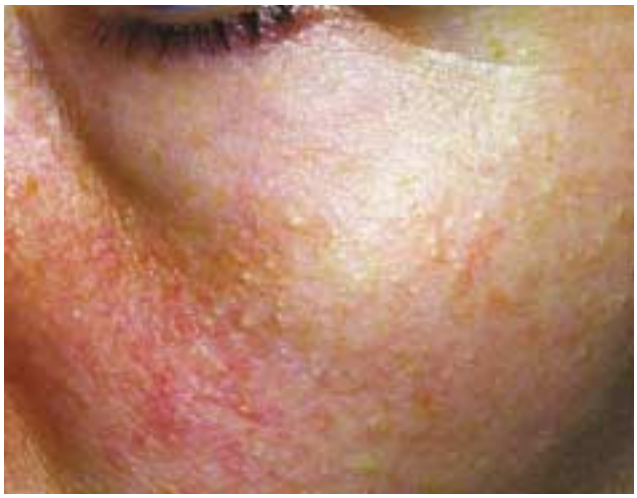
Comedones in which the pore (orifice of the duct) is open and wide are called blackheads (the colour is due to the pigment melanin, not dirt!). Those in which the duct is narrowed and the pore barely visible are called whiteheads (Fig. 4). Tiny whiteheads or microcomedones



RIGHT:
Fig. 1. Spots can wipe the smile off even a 10-year-old's face. The first signs of acne are often present at this age.

FAR RIGHT:
Fig. 2. Well established acne in an adult male. Note the presence of both inflammatory lesions and blackheads.

PHOTOS COURTESY SKIN RESEARCH CENTRE, LEEDS



TOP LEFT:
Fig. 3. The heterogeneous 'Sebutape' pattern of a 9-year-old girl who already has numerous whiteheads. Each dot represents the sebum output from a single pilosebaceous follicle. Note the presence of 'gushers'. At this stage, propionibacteria are absent.

LOWER LEFT:
Fig. 4. Numerous comedones (whiteheads) on the cheek of a teenager.

BELOW:
Fig. 5. Colonies of all three species of cutaneous propionibacteria (*P. acnes*, *P. granulosum* and *P. avidum*) as obtained from a scrub wash of adult facial skin. The colony colour is due to porphyrins.

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are often referred to as acne timebombs. These spots are too small for most people to be aware of, but can rapidly transform into inflamed lesions when the third and final participants in the acne triad, the resident skin microbes *Propionibacterium acnes* and/or *Propionibacterium granulosum* (Fig. 5) trigger a powerful immune response, mediated by CD4+ve T cells. Although the organisms appear to be sebum-dependent *in vivo* (numbers are low where sebaceous glands are sparse), they have no requirement for lipid *in vitro*.

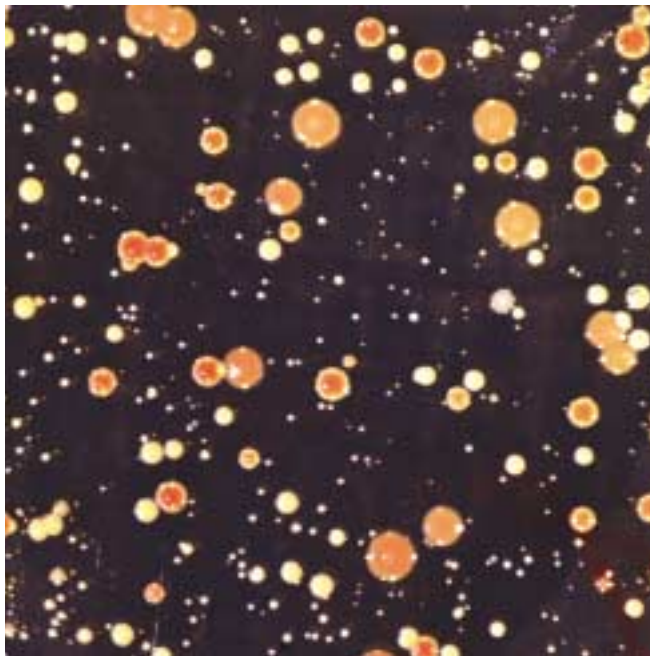
The role of proprionibacteria

What makes harmless skin commensals suddenly turn into bad guys? The truth is that we don't know for sure. In acne-prone individuals, numbers of propionibacteria on the skin surface rise during puberty and reach adult levels by the mid-teens. In non-acne subjects, numbers remain low throughout puberty and rise in the late teens, not reaching adult levels until the age of 20. Sebum output is rising throughout this period. At the follicular level, there is something of a paradox. In mature subjects without acne, most pilosebaceous follicles (Fig. 6) contain viable propionibacteria. In contrast, only a minority of normal follicles in acne patients contain the organisms, although a majority of lesions (both inflamed and non-inflamed) do so.

Cutaneous propionibacteria are slow-growing microaerophiles and may be unable to colonize follicles in which the sebum excretion rate is high. When such follicles become functionally blocked, sebum production (and oxygen tension) is reduced, possibly via a feedback mechanism. This may allow organisms trapped within the follicle to multiply. In normal (unblocked) follicles, end products of bacterial metabolism escape with the outflowing sebum. This is called an open or continuous culture system and is like the intestinal tract in which nutrients enter at one end and bacteria plus their metabolites exit at the other. When a follicle becomes blocked, it behaves as a closed or batch culture system from which bacteria and their end products cannot escape. It is probably the build up of these products to toxic levels that damages the follicle wall and/or initiates the inflammatory response. Bacteria will also die and lyse *in situ*, releasing their intracellular contents and highly antigenic cell wall fragments into the duct.

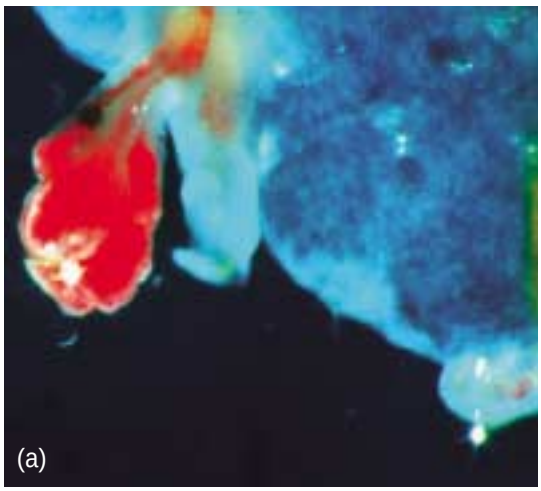
The immune response in acne

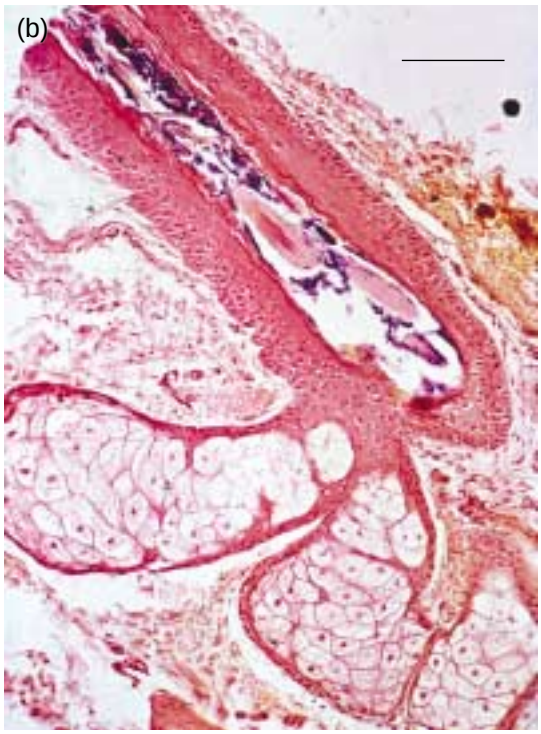
The cellular infiltrate around inflamed acne lesions is characteristic of a delayed type hypersensitivity response, presumably to one or more lesional antigens, not necessarily propionibacterial. Damage to the follicle wall will allow non-bacterial antigens to escape into the dermis. The immune response in acne, particularly severe acne (characterized by granulatomous nodular lesions) is similar to that seen in tuberculosis. Like mycobacteria, *P. acnes* and *P. granulosum* exhibit potent adjuvant activity and non-specifically up-regulate macrophage functions, including recruitment of Th1 cells which recognize not only propionibacterial, but also co-antigen-specific proteins displayed on the surface of the macrophages themselves or on Langerhans (antigen-presenting) cells. Such co-antigens may be keratinocyte-derived. Adjuvant activity is strain-variable and correlates with the ability to persist within macrophages. *P. acnes* has been implicated in a number of other chronic inflammatory diseases, including sarcoidosis, periodontitis, the SAPHO syndrome (characterized by sterno-clavicular osteoarthritis and isolation of the organism from bone biopsies) and, most recently, sciatica.



Prediction and prevention

Research over the last 30 years has done much to increase our understanding of what causes spots and we have now reached a point where predicting and preventing





LEFT:
Fig. 6. Single pilosebaceous follicles. (a) Fresh biopsy specimen stained with Oil Red O to visualize lipid and (b) lateral section to show the multilobular sebaceous gland and the pilosebaceous duct (bar, 100 μm).
PHOTOS COURTESY SKIN RESEARCH CENTRE, LEEDS

acne (or at least reducing its severity) are no longer unrealistic possibilities.

As already noted, acne spots, particularly whiteheads, start to appear during the adrenarche and prior to puberty. The earlier the appearance of such lesions, the worse the acne is likely to be. Here in Leeds, 'Sebutapes' are being used to assess sebum production at 6-monthly intervals in a cohort of primary schoolchildren. A simple biopsy method using cyanoacrylate glue on a glass slide is being used in parallel to detect and enumerate follicular casts. Casts are the plugs which block some follicles. Colonization by, and population densities of, cutaneous propionibacteria are being monitored using a surface scrub wash method followed by viable counting on selective medium. The presence and number of inflamed and non-inflamed lesions on the face and trunk is recorded at each visit. Developmental stage is determined by the estimation of DHEAS in saliva and by recording physical signs (Tanner stage). The aim is to follow each child through puberty to see whether any of the tests will accurately detect acne proneness. If we identify a reliable predictive test, then we may be able to offer at risk children early intervention to either prevent the spots forming or reduce the severity of disease.

We can do this in two ways. First, a topical retinoid (a derivative of vitamin A available on prescription) can be used to prevent pores becoming blocked. Second, propionibacterial colonization can be delayed by the use of a topical antibacterial agent such as benzoyl peroxide (available over the counter). A combination of the two may be the best strategy, but there is a fundamental problem. Both types of product have low cosmetic acceptability and getting children without spots to use such products regularly for several years is a tall order for any parent. Their use would have to become a ritual just like brushing teeth morning and evening. What about those children who will get acne on their trunk? It is very difficult to apply topical products to these areas and preventative strategies based on existing topical products are unlikely to be successful.

For the vast majority of children prevention is not yet a realistic option and the spots will appear anyway. Acne should always be treated early and aggressively to minimize the risk of physical and emotional scarring. A wide range of safe and effective therapies is available on prescription. Boys are more reluctant to seek medical help than girls, despite the fact that they tend to suffer from more severe disease. Young Alice was right – any child with inflamed spots or lots of whiteheads should be taken to see their family doctor at the earliest opportunity.

Is acne all bad news?

Many experts have theorized as to why humans get acne. If the biological role of acne is to modulate physical attractiveness, with the more spotty males and females less likely to find a mate, then one might assume some kind of genetic linkage between spottiness and at least one other deleterious trait.

Some light may come from an unexpected source. In 1991/2, over 14,000 mothers-to-be were enrolled to the Avon Longitudinal Study of Parents and Children (http://www.ich.bris.ac.uk/ALSPAC). Every detail of these pregnancies was meticulously documented by Professor Jean Golding and her team at the University of Bristol. Live births have been followed up annually with detailed questionnaires and regular physical examinations. The children are now approaching puberty and will provide an invaluable resource for examining the effects of nature versus nurture on acne proneness and to uncover any linkages between acne and other heritable traits. There is already evidence that multiple genetic loci are involved in modulating sebum excretion.

The natural assumption is that spots are bad news, but what if there were advantages to having acne? Because propionibacteria are potent adjuvants, their presence on human skin may constitute a first line immune defence system against microbial infection and cancer. Acne, by enhancing systemic exposure to immunostimulatory

Further reading

Eady, E. A. & Cove, J. H. (2000). Is acne an infection of blocked pilosebaceous follicles? *Am J Clin Dermatol* 1, 201–209.

Ingham, E. (1999). The immunology of *Propionibacterium acnes* and acne. *Curr Opin Infect Dis* 12, 191–197.

Lucky, A. W., Biro, F. M., Huster, G. A., Leach, A. D., Morrison, J. A. & Ratterman, J. (1994). Acne vulgaris in premenarchal girls. An early sign of puberty associated with rising levels of dehydroepiandrosterone. *Arch Dermatol* 130, 308–314.

Pierard, G. & Pierard-Franchimont, C. (1992). The Sebutape technique for monitoring androgen dependent disorders. *Eur J Med* 1, 109–112.

Vlajinac, H. D., Adanja, B. J., Lazar, Z. F., Bogavac, A. N., Bjekic, M. D., Marinovic, J. M. & Kovec, N. I. (2000). Risk factors for basal cell carcinoma. *Acta Oncol* 39, 611–616.

components of the organisms, may upregulate their protective effect and extend it beyond the skin. Studies in animal models have revealed that *P. acnes* promotes a Th1-type response to tumours, viruses, parasites and facultative intracellular bacterial infections. There is already evidence that two skin tumours, basal cell carcinoma and malignant melanoma, are less common amongst past acne sufferers than age- and sex-matched non-acne subjects. The organisms have been successfully used to treat certain advanced cancers, especially of the bladder. Acne may simply be the price we pay for the optimum performance of a natural defence mechanism. If acne is slowly but surely eliminated, we may begin to pay a much higher price as the incidence of certain cancers starts to rise. One day we may all be popping pills of *P. acnes* in a bid to stay healthy.

Help for acne sufferers

Concerned teenagers or parents may wish to know how to contact the Acne Support Group. Their address is PO Box 230, Hayes, Middlesex UB4 0UT (Tel/Fax: 0181 561 6868).

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Letter from the President – 'Local Representatives' for SGM

Dear Member

Since becoming President of the SGM a year ago I have been increasingly impressed by the range of services that the Society provides to microbiologists and microbiology, especially in the UK, but also internationally. During my term of office I aim to help increase the Society's impact even further, building, of course, on the efforts of my predecessor, Howard Dalton, and the huge energies and experience of the Officers, Council and Staff.

There have been a number of recent initiatives.

- The Society has started several new **grant and fellowship schemes** for members, especially, but not exclusively, younger microbiologists at an early stage in their careers.
- We have increased the number of **Groups** in the Society to cover different areas of microbiology, adding Clinical Microbiology, Food and Beverages, and Eukaryotic Microbes to the set of ten already in existence. This means that our two **meetings** each year are becoming increasingly busy and exciting.
- We are fostering **education** in microbiology, right through from primary school to university level, by producing teaching materials, providing a category of schools membership, and in many other ways.
- We are now better equipped to make representations on microbiological matters to government, the public, and indeed anyone who will listen, with a full-time staff member dealing with **public affairs**.
- We will soon be publishing four **journals** covering a very wide range of microbiological fields. Our taking over of the *International Journal of Systematic Bacteriology* (formerly the published by the American Society for Microbiology and now the *International Journal of Systematic and Evolutionary Microbiology*), is to be followed by the *Journal of Medical Microbiology*, a gift from the Pathological Society.
- And of course we also publish *Microbiology Today*, the award-winning quarterly **magazine** of the Society.

One way in which we can pursue the SGM aim of becoming even more visible and relevant is to identify a Local Representative in every university or college department, or research institute, hospital or company, which teaches or uses microbiology. Such a person could act as a two-way conduit between the Council, Officers and Staff on the one hand and every member or, more importantly, potential member on the other. I do not envisage a rigid and precisely defined role for the Local Representatives. It will be a chance to be imaginative and pro-active, according to local circumstances. However, one important function will be to make sure that as many as possible of the eligible microbiologists in each institution are aware of the advantages of membership of the SGM, realize what good value for money membership can provide, and join the Society.

This is why I am writing to you now. Even if you do not wish to volunteer personally, I hope you will be able to think about who in your organization might be really suited to the task, and to persuade them to get in touch with Janet Hurst, our Deputy Executive Secretary at Marlborough House (Tel. 0118 988 1809; email j.hurst@sgm.ac.uk), who will co-ordinate the activities of the Local Representatives.

Further information about the Society, listing its many activities and benefits of membership, is on our website at www.sgm.ac.uk

Thank you for reading this letter. We look forward very much to hearing from your institution.

Collegiate regards

David Hopwood

Please note that this letter has also been sent individually to possible representatives in a number of institutions but we are seeking volunteers to make the coverage as complete as possible.