



The ROYAL  
SOCIETY of  
MEDICINE

BRSM

## JOURNAL OF THE ROYAL SOCIETY OF MEDICINE

March 1997

Volume 90

Number 3

ISSN 0141-0768

### Editorials

Hazards of growing up  
Growth hormone for adults

### Issue of the day

Are you competent with congenital heart disease?

### Original articles

Death in heart disease  
Intestinal stenting to prevent adhesional obstruction  
Cardiac investigations before renal transplantation

### Review articles

Why has stroke mortality been falling?  
Rosacea  
Economics of laboratory testing

### Case reports

Eye drops and lethargy  
Long-term hypercalcaemia in sarcoidosis  
Lump in the groin—orthopaedic  
Kasabach–Merritt and Down's  
Enterocutaneous fistula in an Ethiopian

### Misleading presentation

Chilblains or cancer

### History

The missing doctor

### Personal papers

Airships, space shuttles, and biologicals  
The treasures of Blythe House

### Art in hospitals

The Gabo Fountain at St Thomas'

### Book of the month

Evolutionary psychiatry

### Letters

Complementary medicine in the curriculum • useful plants •  
Community hospitals • Hospital-at-home • Save the ESR • Sailors,  
scurvy and science • *Helicobacter pylori* infection

Univ. of Minn.  
Bio-Medical  
Library

3 24 97

Published by The Royal Society of Medicine 1 Wimpole Street London

Dr. Reddy's Laboratories, Ltd., et al.  
v.  
Galderma Laboratories, Inc.  
IPR2015



The ROYAL  
SOCIETY of  
MEDICINE

JRSM

## JOURNAL OF THE ROYAL SOCIETY OF MEDICINE

March 1997

Volume 90

Number 3

ISSN 0141-0768

### Editorials

Hazards of growing up  
Growth hormone for adults

### Issue of the day

Are you competent with congenital heart disease?

### Original articles

Death in heart disease  
Intestinal stenting to prevent adhesional obstruction  
Cardiac investigations before renal transplantation

### Review articles

Why has stroke mortality been falling?  
Rosacea  
Economics of laboratory testing

### Case reports

Eye drops and lethargy  
Long-term hypercalcaemia in sarcoidosis  
Lump in the groin—orthopaedic  
Kasabach–Merritt and Down's  
Enterocutaneous fistula in an Ethiopian

### Misleading presentation

Chilblains or cancer

### History

The missing doctor

### Personal papers

Airships, space shuttles, and biologicals  
The treasures of Blythe House

### Art in hospitals

The Gabo Fountain at St Thomas'

### Book of the month

Evolutionary psychiatry

### Letters

Complementary medicine in the curriculum • useful plants •  
Community hospitals • Hospital-at-home • Save the ESR • Sailors,  
scurvy and science • *Helicobacter pylori* infection

Univ. of Minn.  
Bio-Medical  
Library

3 24 97

Published by The Royal Society of Medicine 1 Wimpole Street London W1M 8AE

## Rosacea: classification and treatment

Thomas Jansen MD Gerd Plewig MD

*J R Soc Med* 1997;90:144-150

Rosacea is a chronic skin disorder affecting the facial convexities, characterized by frequent flushing, persistent erythema, and telangiectases. During episodes of inflammation additional features are swelling, papules and pustules. The disease was originally called acne rosacea, a misleading term that unfortunately persists<sup>1</sup>.

Rosacea is a common disease, especially in fair-skinned people of Celtic and northern European heritage; it has been called the curse of the Celts. It is rare in American and African blacks<sup>2</sup>. Women are more often affected than men, but they seldom suffer the gross tissue and sebaceous gland hyperplasia of rhinophyma. Onset is usually between ages 30 and 50. In a recent epidemiological study the prevalence was 10%, most of the patients having only a red face<sup>3</sup>. In young patients especially, there may be a history of acne and the conditions may coexist.

### **PATHOGENESIS**

The exact aetiology of rosacea is unknown and theories abound<sup>4</sup>. Gastrointestinal disturbances, notably dyspepsia with gastric hypochlorhydria, were long suspected of being a causal factor, but controlled investigations with a gastrocamera<sup>5</sup> and biopsy studies<sup>6</sup> revealed no association. *Helicobacter pylori* has come under suspicion, but results are conflicting<sup>7</sup>. For example, Powell *et al.*<sup>8</sup> found *H. pylori* antibody in 19 of 20 patients, while Schneider *et al.*<sup>9</sup> found no statistical difference in positivity between patients (49%) and controls (43%). Psychogenic factors have been frequently implicated but there is no good evidence that the condition is associated with personality type or is precipitated by emotional disturbance.

The theory of hypersensitivity to *Demodex folliculorum* or its products is based primarily on the distribution of rosacea and the mite, the follicular nature of rosacea, and the finding of the mite in areas of acute inflammation in some cases of rosacea<sup>10</sup>. However, *D. folliculorum* mites are normal inhabitants of human follicles and sebaceous glands and application of 3% sulphur ointment, while resulting in clinical improvement of rosacea, did not affect the *Demodex* population<sup>11</sup>. At most, the mite induces papule or pustule

formation in pre-existing rosacea. Rosacea was once regarded as a seborrhoeic disease. Seborrhoea is, however, not always present<sup>12</sup>. Unlike acne vulgaris, rosacea is not primarily a disease of sebaceous follicles.

The pathogenesis of rosacea thus remains obscure. What is certain, however, is that rosacea patients are constitutionally predisposed to blushing and flushing. The basic abnormality seems to be a microcirculatory disturbance of the function of the facial angular veins<sup>13</sup>. Statistical associations between rosacea-related flushing and migraine suggest a shared disorder of vascular regulation<sup>14</sup> but there is no direct evidence that rosacea is primarily a vascular disorder. The response of the facial vessels to adrenaline, histamine and acetylcholine is normal,<sup>15</sup> and the vessels do not seem abnormally fragile<sup>16</sup> so the main abnormality is probably in the dermis surrounding blood vessels rather than in vessel walls. In addition, the distribution of rosacea is not identical with the flush area. A very important background feature is sun damage. Rosacea is always associated with solar elastosis and often with heliodermatitis<sup>17</sup>. Fair-skinned patients with rosacea type I will often give a history of sun sensitivity.

### **CLINICAL FINDINGS**

Rosacea is usually symmetrically distributed over the face and is particularly obvious over the nose, cheeks, chin, forehead, and glabella. Occasionally, lesions are seen at extrafacial sites including the retroauricular areas, the V-shaped area of the chest, the neck, the back, and the scalp and extremities<sup>18</sup>. The hallmarks of rosacea are papules and papulopustules, vivid-red erythema, and telangiectases and a history of flushing. Comedones are notably absent. In severe cases papules are numerous enough to be confluent. Granulomatous changes can develop in later stages, sometimes receiving special designations such as lupoid rosacea. Rhinophyma and other phymas are the ultimate tissue reactions. For didactic but also for therapeutic reasons rosacea is classified into stages and grades. The progression is not inevitable, and few patients experience the full course of the disease.

### **Episodic erythema**

Most rosacea patients react with transient erythema on the

Department of Dermatology, Ludwig-Maximilians-University, Frauenlobstrasse

predisposed to blushing and flushing (rosacea diathesis). The reactions are more frequent and more easily induced than ordinary blushing. Numerous non-specific stimuli such as ultraviolet radiation, heat, cold, chemical irritation, strong emotions, alcoholic beverages, hot drinks, and spicy food can trigger these flares. It is a mistaken belief that tea and coffee are precipitants; the specific stimulus is heat<sup>19</sup>. Among the mediators proposed to be involved in the erythematous response are substance P, histamine, serotonin, and prostaglandins but the trigger remains unknown.

### Stage I

The erythema persists for hours and days, hence the old description erythema congestivum. Erythema lasting only a few minutes is not early rosacea. Telangiectases become progressively more prominent, forming sprays on the nose, nasolabial folds, cheeks, and glabella. Most patients complain of sensitive skin that stings and burns after application of cosmetics, fragrances, and certain sunscreens. Trauma from abrasives and peeling agents readily induces long-lasting erythema. Thus the facial skin is unusually vulnerable to chemical and physical stimuli.

### Stage II

Inflammatory papules and pustules develop and persist for weeks. Some papules show a small pustule at the top. The lesions are always follicular in origin—mainly sebaceous follicles but also the smaller and more numerous hair follicles. The deeper inflammatory lesions may heal with scarring, but scars are small and tend to be shallow. Facial pores become larger and more prominent. If there has been heavy solar exposure for decades, the stigmata of photo-damage become superimposed—namely elastosis, solar comedones, and heliodermatitis. The papulopustular attacks become more frequent. Rosacea may extend over the entire face and even spread to the scalp, especially if the patient is balding. Itchy follicular pustules of the scalp are typical. Bacteriological studies of these pustules reveal nothing of interest. Finally the sides of the neck and the retroauricular and presternal area may be affected. Even the palms may show persistent erythema.

### Stage III

A small proportion of patients progress to the worst expressions of the disease—namely, large inflammatory nodules, furunculoid infiltrations, and tissue hyperplasia. These derangements occur particularly on the cheeks and nose, less often on the chin, forehead, or ears. The facial contours become coarse, thickened, and irregular. Finally

*d'orange*). These coarse features are due to inflammatory infiltration, connective tissue hypertrophy with masses of collagen deposition, diffuse sebaceous gland hyperplasia, and overgrowth of individual sebaceous glands forming dozens of yellowish umbilicated papules on cheeks, forehead, temples and nose. Thickened folds and ridges create a grotesque appearance resembling the leonine facies of leprosy. The ultimate deformities are the phymas, of which rhinophyma is the archetype.

## ROSACEA VARIANTS

The diagnosis of rosacea in its classic forms presents no difficulty. The variants, however, may be overlooked or misdiagnosed.

### Persistent oedema of rosacea

The published work hardly mentions this distressing variant. It has been reported as Morbihan disease or rosaceous lymphoedema<sup>20,21</sup>. A hard non-pitting swelling is found on the areas involved, mainly on the forehead, glabella, nose, or cheeks. A similar oedema sometimes arises in acne and in the Melkersson-Rosenthal syndrome; it develops against a background of chronic inflammation of any cause, including bacterial infection.

### Ophthalmic rosacea

Eye involvement is surprisingly common. Indeed, the disease may begin in the eye and escape diagnosis for a long time. The ophthalmic signs include blepharitis, conjunctivitis, iritis, iridocyclitis, hypopyon-iritis, and even keratitis<sup>22</sup>. The term ophthalmic rosacea covers all these signs. The incidence is not known but more than half of patients participating in a cooperative isotretinoin trial for the treatment of rosacea were diagnosed by ophthalmologists as having inflammatory eye involvement<sup>23</sup>, blepharitis and conjunctivitis being the most common. The ophthalmic complications are independent of the severity of the facial rosacea but there is a strong correlation between the degree of eye involvement and a tendency to flushing<sup>24</sup>. Rosacea keratitis has an unfavourable prognosis, and in extreme cases leads to corneal opacity and blindness. Perhaps the most frequent eye sign is chronically inflamed margins of the eyelids, with scales and crusts, quite similar to seborrhoeic dermatitis, with which it is often confused. Pain and photophobia may be present. All patients with progressive rosacea should be seen by an ophthalmologist.

### Lupoid or granulomatous rosacea

Some patients develop epithelioid (lupoid) granulomas in a diffuse pattern<sup>25</sup>. Clinically, dozens of brown-red papules or



shows perifollicular and perivascular granulomas. The concept of a rosacea-like tuberculide of Lewandowsky was based only on the tuberculoid structure found histologically in many papules; however, the condition is probably unrelated to tuberculosis. Its course is chronic and unremitting. Differential diagnosis includes lupoid perioral dermatitis, lupoid steroid rosacea, and micronodular sarcoidosis.

### **Steroid rosacea**

When a rosacea patient is erroneously treated with topical steroids the disorder may at first respond, but the improvement will be followed by steroid atrophy with thinning of the skin and an increase in telangiectases<sup>26</sup>. The complexion becomes dark-red with a copper-like tone. Soon the surface becomes studded with follicular, round, deep papulopustules and firm nodules. The appearance is shocking, with a flaming red, scaling, papule-covered face. The distribution can extend over the entire area of application of the topical steroid, often up to the hairline. Steroid rosacea is a pitiable, avoidable condition which in addition to disfigurement is accompanied by severe discomfort and pain. Withdrawal of the steroid is followed by exacerbation of the disease.

### **Gram-negative rosacea**

This is a newcomer among Gram-negative infections<sup>27</sup>. Clinically it looks like stage II or III disease. Multiple tiny yellow pustules (type I) or deep-seated nodules (type II) increase suspicion. Neither oral antibiotics nor metronidazole will control it. The diagnosis rests on demonstration of Gram-negative organisms by culturing the contents of several pustules. The disease is analogous to Gram-negative folliculitis which sometimes develops on top of acne vulgaris<sup>28</sup>. The organisms are the same: *Klebsiella*, *Proteus*, *Escherichia coli*, *Pseudomonas*, *Acinetobacter*, and others.

### **Rosacea conglobata**

Rarely a patient with severe rosacea shows a reaction that mimics acne conglobata, with haemorrhagic nodular abscesses and indurated plaques. The course is progressive and chronic. This variant mainly occurs in women. It may be provoked by oral ingestion of halogen-containing preparations. Diagnostic features are pre-existing rosacea and limitation to the face, with no other signs of acne conglobata on back, chest, shoulders, or extremities.

### **Rosacea fulminans**

This variant was first described by O'Leary and Kierland<sup>29</sup> under the designation pyoderma faciale. It has been a matter

of rosacea fulminans was coined by analogy with its acne counterpart, acne fulminans<sup>30,31</sup>. This is a conglobate, nodular disease springing up abruptly on the face of young females. Curiously, it does not occur in males. Rosacea fulminans is confined to the face. Once seen it is never forgotten. Monstrous coalescent nodules and confluent draining sinuses occupy most of the face. The main locations are the chin, cheeks, and forehead. Ripe abscesses form with multiple pustules riding on top of the carbunculoid nodules. The face is diffusely reddened. Seborrhoea is a constant feature but may be overlooked. When questioned closely, patients will often describe the development of oiliness before the onset. Previous acne or rosacea is usually denied; however, we perceived a connection to rosacea because, after the stormy blow-up, signs of rosacea often make their appearance. Some patients, too, have been flushers and blushers. Aetiology remains obscure. Often blamed is severe emotional stress, such as the death of a family member, divorce, or loss of a lover, but some patients are stress-free. The prognosis is excellent. Once the disease has been brought under control it does not recur. Differential diagnosis includes acne conglobata (young patients, mostly males, longer history, other signs of acne, comedones, scars, seborrhoea, no flushing or blushing), acne fulminans (usually seen in teenage boys), bromoderma, iododerma, and virilizing tumours.

### **PHYMAS IN ROSACEA**

Phyma is the Greek word for swelling, mass, or bulb. Phymas occur in various areas of the face and ears, rhinophyma (rhinos=nose) being the commonest. It occurs exclusively in men and fortunately it is a rare complication. Rhinophyma may be perceived by the public as due to excessive alcohol consumption, as in the comedian W C Fields. The bulbous nose develops over many years as a result of progressive increase in connective tissue, sebaceous gland hyperplasia, ectatic veins, and chronic deep inflammation. Rhinophyma may accompany stage III rosacea but in some patients the signs of rosacea in the rest of the face are surprisingly mild. Four variants of rhinophyma can be recognized. In the glandular form, the nose is enlarged mainly because of enormous lobular sebaceous gland hyperplasia. The surface is pitted, with deeply indented and mildly distorted follicular orifices. The tumorous expansions of the nose are often asymmetrical and of varying size. Humps and sulci occur. Sebum excretion is increased. Compression by the fingers yields a white pasty substance consisting of an amalgam of corneocytes, sebum, bacteria, and sometimes *Demodex* mites. In the fibrous form, diffuse hyperplasia of the

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.