

---

# ADVANCES IN Dermatology®

---

VOLUME 17

**Editor-in-Chief**

**William D. James, MD**

Albert M. Kligman Professor of Dermatology, Director of Resident Program and Faculty Clinic, University of Pennsylvania School of Medicine, Philadelphia

**Associate Editors**

**Clay J. Cockerell, MD**

Director, Division of Dermatopathology, Clinical Professor of Pathology and Dermatology, University of Texas Southwestern Medical Center, Dallas

**Mary E. Maloney, MD**

Professor of Medicine (Dermatology), Clinical Division Chief and Director of Dermatological Surgery, University of Massachusetts Medical School, Worcester

**Amy S. Paller, MD**

Professor of Pediatrics and Dermatology, Northwestern University Medical School; Head, Division of Dermatology, Children's Memorial Hospital, Chicago

**Kim B. Yancey, MD**

Professor and Chair, Department of Dermatology, Medical College of Wisconsin, Milwaukee

 **Mosby**

**DOCKET  
ALARM**

Find authenticated court documents without watermarks at [docketalarm.com](http://docketalarm.com).



*Publisher:* Cynthia Baudendistel  
*Developmental Editor:* Victoria Cernich  
*Manager, Continuity Production:* Idelle L. Winer  
*Senior Production Editor:* Pat Costigan  
*Project Supervisor, Production:* Joy Moore  
*Composition Specialist, Production:* Betty Dockins

Copyright © 2001 by Mosby, Inc

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without prior written permission from the publisher.

Permission to photocopy or reproduce solely for internal or personal use is permitted for libraries or other users registered with the Copyright Clearance Center, provided that the base fee of \$35.00 per chapter is paid directly to the Copyright Clearance Center, 21 Congress Street, Salem, MA 01970. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collected works, or for resale.

Printed in the United States of America  
Composition by Thomas Technology Solutions, Inc  
Printing/binding by the Maple-Vail Book Manufacturing Group

Editorial Office:  
Mosby, Inc  
11830 Westline Industrial Drive  
St Louis, MO 63146  
Customer Service: [hhspscsharcourt.com](mailto:hhspscsharcourt.com)

International Standard Serial Number: 0882-0880  
International Standard Book Number: 0-323-01535-2

# C

## CHAPTER 2

# Pathogenesis of Rosacea

**Mark V. Dahl, MD**

Professor and Chairman, Department of Dermatology, Mayo Clinic  
Scottsdale, Scottsdale, Ariz

### EDITOR'S COMMENT

Rosacea is a source of constant embarrassment and worry for our affected patients. Bright red cheeks, enlarged noses, and erythematous papules and pustules interfere with social and occupational interactions. Depression, anxiety, and inferences about alcoholism haunt sufferers of this fiery disease. To compound their misery, very few hard data exist regarding the etiopathogenesis of rosacea. Dr Mark Dahl, who has a long interest in helping alleviate the effects of this illness, shares his insights in this superbly written article. Mark separates rosacea into several subsets of specific findings. Explanations behind the appearance of each of them are reviewed. In the concluding section, a unifying concept is proposed to bring all of these contributing factors into focus and explain the totality of the signs and symptoms of this chronic and very public disease. Expanding this knowledge base and using our discoveries to improve therapy are goals we look forward to being realized.

*William D. James, MD*

**R**osacea is a disease composed of many elements or subsets. Rosacea is more like a syndrome than a single disease. Although all patients with rosacea develop some erythema of their skin, not all patients develop all other stigmata. Some patients have centrofacial flushing and edema. Others are more troubled by papules and pustules. Still others are more troubled by burning and stinging sensations, or by rhinophyma. Subsets of rosacea are listed in Table 1.

The cause of the rosacea complex is unknown, and unifying hypotheses are speculative. Whatever the cause, facial skin is

**TABLE 1.**  
Subsets of Rosacea

---

Erythema
Flushing
Edema
Papules and pustules
Telangiectasias
Stinging and burning sensations
Rosacea dermatitis
Rosacea cellulitis
Fibrosis/rhinophyma

---

predisposed. The disease affects only the facial skin and cornea. The tip of the nose is affected first, followed sequentially by the cheeks, forehead, and chin.

## ERYTHEMA

Many people have ruddy complexions. Not all of these people have rosacea. The ruddy erythema of rosacea tends to persist (erythema congestivum) and usually waxes and wanes markedly in response to changes of body temperature, ingestion of certain foods, evoked emotions, or other factors. Sometimes the erythema involves the whole face, but more often it involves just the central face. Erythema is often striped by telangiectatic blood vessels.

A red complexion characterizes people of European extraction, particularly Celts. In addition to this obvious genetic element, erythema is more pronounced in some families than in others. The amount of blood in the facial skin and blood vessels is high. Total movement of red blood cells in flush areas of rosacea skin is 3 to 5 times higher than in controls.<sup>1</sup>

Finally, the erythema of rosacea seems aggravated by chronic sun exposure and photodamage. People without rosacea can develop poikiloderma of Civatte (erythromelanosis coli), and this same propensity toward erythema and telangiectasia seems to augment the baseline erythema among patients with rosacea and lightly pigmented skin. Solar damage is not a prerequisite for the development of rosacea.<sup>2,3</sup> Patients with rosacea are not more prone to sunburn.<sup>4</sup>

The blushlike redness that develops on rosacea faces during and after exposure to sunlight is more likely caused by heat from infrared radiation than by photons from ultraviolet radiation. The radiant heat-derived redness develops quickly during (rather than

after) exposure. Exposing facial skin to other sources of radiant heat, such as heat from a fireplace or stove, reproduces it.

Immunofluorescence staining of rosacea skin often finds immunoglobulins, especially IgG and IgM, at the dermal-epidermal junction of sun-damaged skin and facial skin of patients with rosacea. This can be an artifact produced by preserving specimens in Michel's transport media, which seems prone to increase non-specific staining of dermis, dermal-epidermal junction, and blood vessels, especially in sun-damaged skin (unpublished observations). In other patients, the appearance of immunoglobulin deposits at the dermal-epidermal junction (especially in dermal papillae) is an artifact allegedly produced by compression of autofluorescing elastic tissue against the dermal-epidermal junction by edema and dilated papillary dermal blood vessels (Burnham's "fibrillar pseudoband").<sup>5</sup>

Perhaps in others, antibodies bind to sun-damaged connective tissue.<sup>6-9</sup> Circulating IgG and IgM antibodies to collagen, anti-nuclear antibodies, and anti-*Demodex* antibodies have been found in patients' sera. In addition, eluates from autologous circulating lymphocytes in peripheral blood of patients with rosacea have reacted with nuclei of "dermal cells," endothelial cells, and eccrine duct cells.<sup>7</sup>

## FLUSHING

Both flush and erythema occur when blood vessels dilate and blood flow increases in superficial vessels of the skin. Whereas the erythema is chronic and persistent and varies subtly, the flushing can wax and wane quickly. Flushing usually involves the central face and is associated with a warming of surface skin.

Patients with mastocytosis and carcinoid syndrome can develop all the stigmata of rosacea, including ocular rosacea, facial telangiectasia, and connective tissue hypertrophy.<sup>10-12</sup> Flushing can be stimulated by various environmental trigger factors as listed in Table 2.

In hyperthermic, but not normothermic healthy human beings, cool venous blood from the face and scalp enters the dural venous sinus via vascular pathways or emissary veins. The cooler blood intermingling with the brain and meningeal blood vessels keeps the intracranial temperature cool. Brinnel et al<sup>13</sup> found that venous blood flow from the skin to the brain was suppressed in patients with rosacea, thus inhibiting selective brain cooling in hyperthermic conditions. Apparently, the facial skin acts like an automobile radiator to lose heat by radiation, convection, and conduction. In

# 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.