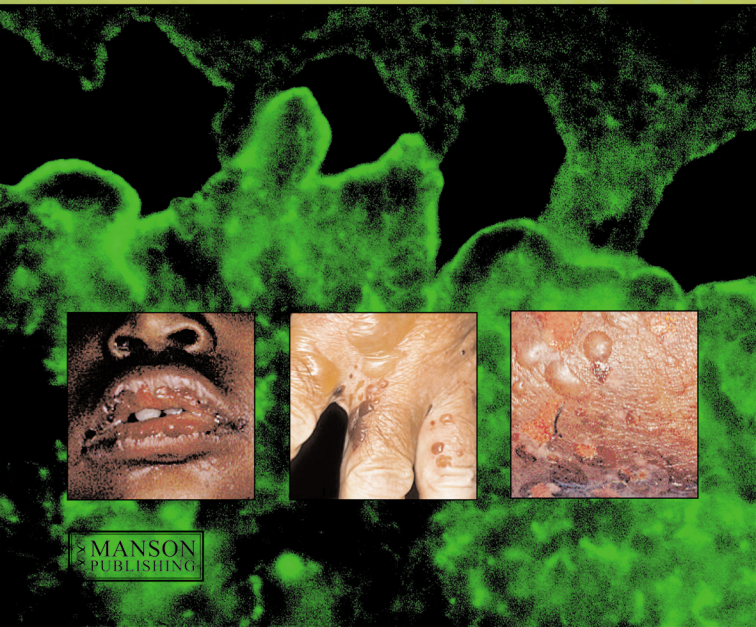
Blistering Skin Diseases

LAWRENCE S. CHAN



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Preface

This book is written for clinical dermatologists, emergency and family physicians, dermatology residents, medical students, and non-physician scientists.

For clinical dermatologists, this book provides concise yet substantial guidelines on the diagnosis and treatment of a range of blistering skin diseases to facilitate the daily care of their patients. The completely up-to-date clinical and laboratory information will allow clinicians to assess the state-of-the-art diagnostic and therapeutic options, and can be used as a resource for continuing medical education. For emergency and family physicians, this book offers a succinct clinical description of different types of blistering diseases and their relative urgency, so that the patients they encounter can be properly treated or referred to appropriate specialists.

For dermatology residents, this book provides a solid foundation for exploring the various aspects of blistering skin diseases, including clinical features, differential diagnoses, laboratory findings, and therapeutic strategy. The sections on pathogenesis will enhance the residents' understanding of molecular events underlying the blistering disease process and assist their preparation for the Dermatology Board examinations.

For medical students, this book opens a window onto the intriguing world of skin diseases that manifest as blisters. It is designed to excite and encourage them to pursue a career in dermatology, or perhaps even a career in academic dermatology.

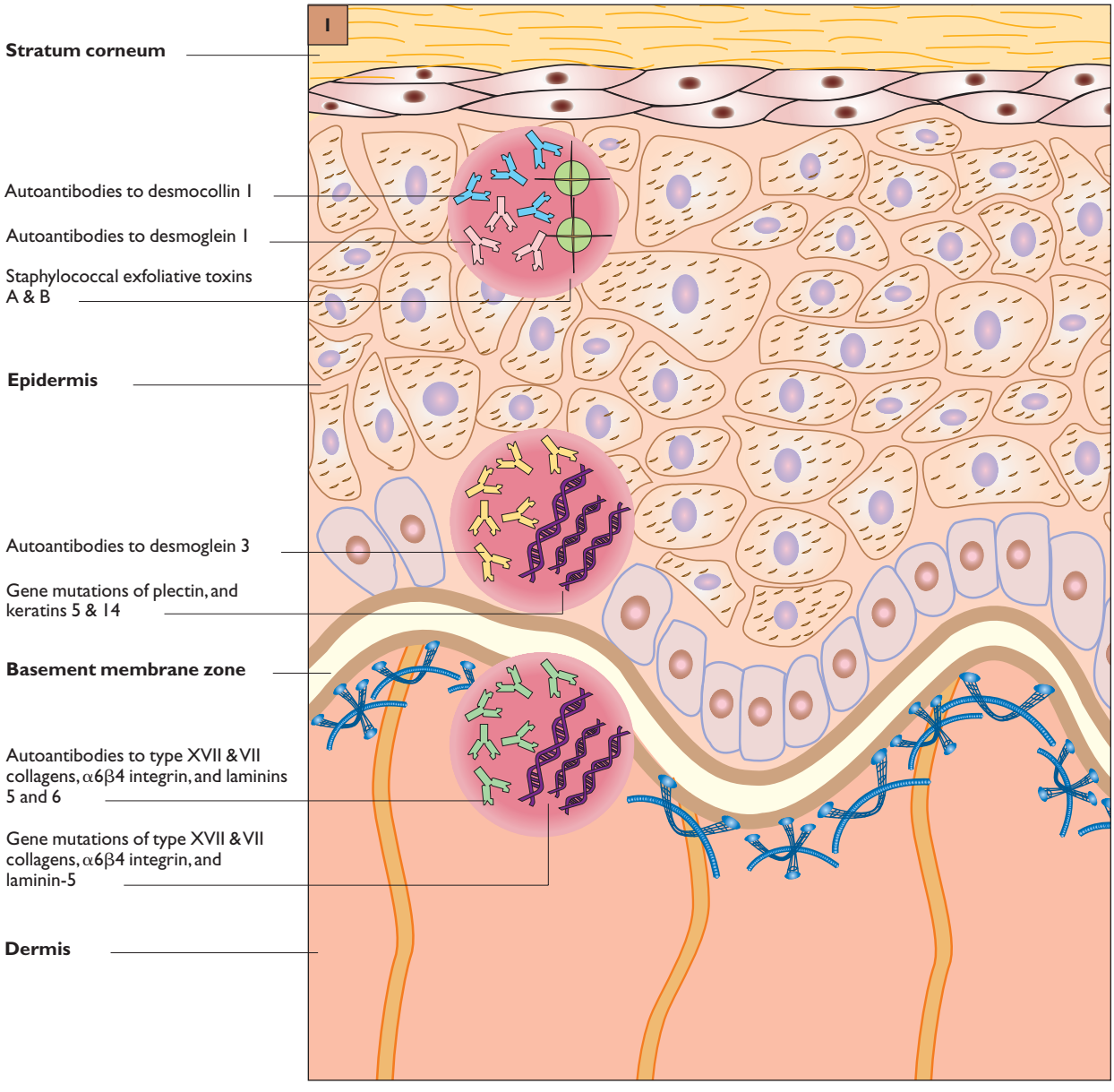
For non-physician scientists, this book bridges the gap between the clinical and basic sciences regarding the pathomechanism of the skin-blistering process. It will hopefully stimulate their interests in the investigation of skin diseases.

Lawrence Chan

AUTHOR BIOGRAPHY

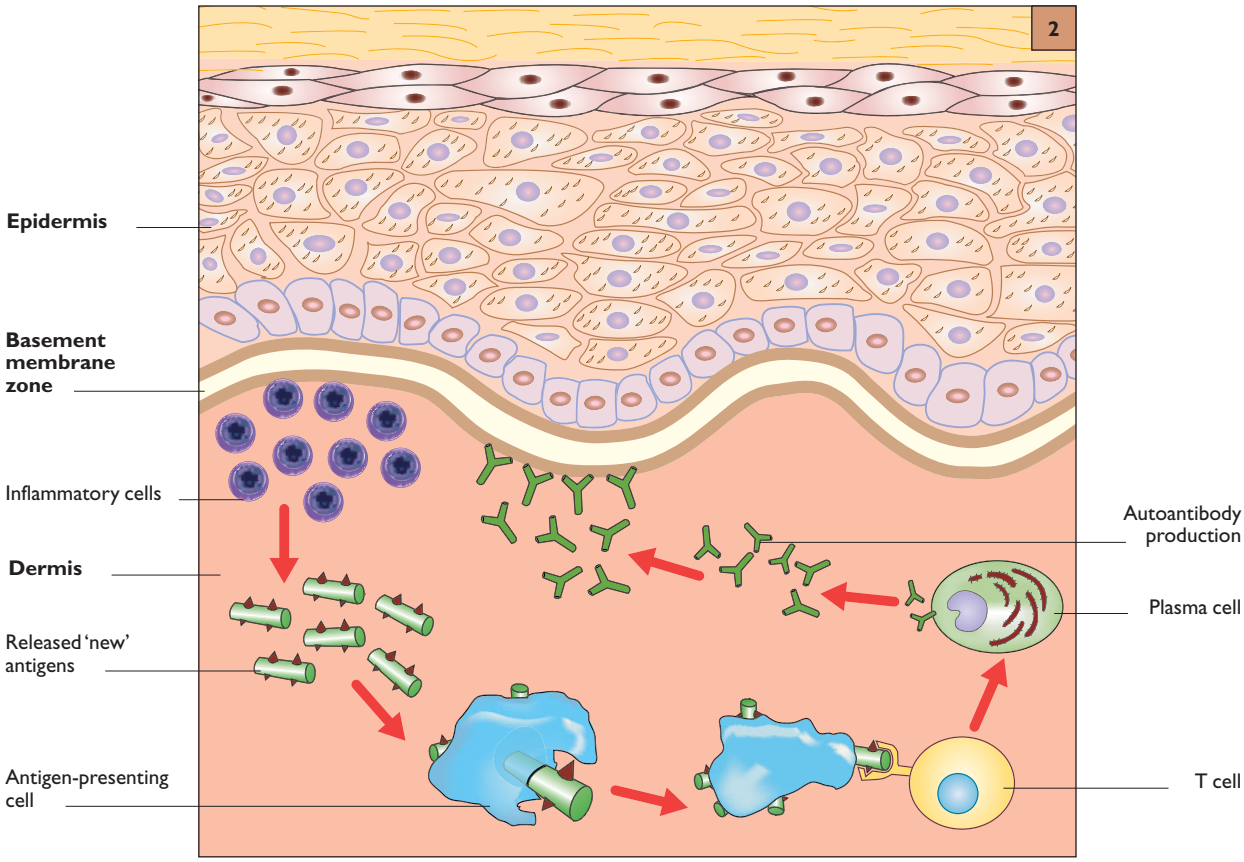
The author, Lawrence S. Chan, M.D., was born in Hong Kong and subsequently immigrated to the United States in 1975. Upon graduation from Massachusetts Institute of Technology with double Bachelor degrees in Chemical Engineering and Life Sciences in 1981, he pursued medicine study at the University of Pennsylvania, School of Medicine, and obtained his M.D. degree in 1985. He served his Medicine Internship at the Cooper Hospital/University Medical Center and his Dermatology Residency and Immuno-dermatology Fellowship at the University of Michigan Medical Center. After a brief faculty position at the Wayne State University School of Medicine, he worked at Northwestern University Medical School as an Assistant Professor of Dermatology and the Director of Immuno-dermatology from 1993 to 2002. Currently, he is a Professor of Dermatology and Microbiology/Immunology and the Director of Skin Immunology Research at the University of Illinois at Chicago, and he is supported by two research grants and one research contract from the National Institutes of Health. Dr. Chan, who also is the Head of the Department of Dermatology at the University of Illinois College of Medicine, has authored and/or coauthored 90 peer-reviewed biomedical journal articles and 30 book chapters, and he was the editor of one scientific textbook.

Overview of blistering skin diseases



MECHANISMS OF BLISTER FORMATION

As a physical barrier protecting humans from external harm, the skin is a structurally complex organ that is made up of many interconnected components. Blisters are formed when one or more of the skin's structural components responsible for functional connection are weakened or destroyed by a variety of mechanisms, including pathogenic autoantibodies, gene mutations, and bacterial toxins (**1**). A major mechanism for causing such weakening is autoimmunity. When pathogenic autoantibodies target one or more of these connecting components, resulting in structural weakening, blisters occur [1; 7]. Examples of such disease entities include pemphigus vulgaris, pemphigus foliaceus, and bullous pemphigoid which are mediated by autoantibodies to desmoglein 3, desmoglein 1, and type-XVII collagen (BP180), respectively. How, then, were pathogenic autoantibodies formed against these critical skin components in the first place? Although there are many possible pathways, one unique pathway that has been seriously considered is 'epitope spreading' (**2**). Evidence which supports the role of 'epitope spreading' is provided by



1 Mechanisms and locations of skin blister formation. Cutaneous components essential for the integrity of skin can be compromised by autoantibodies, protein defect due to gene mutation, and microbial products as depicted here with their target locations.

2 Epitope spreading as a result of chronic inflammation or autoimmune response. New antigenic epitopes can be released from the intact skin as a result of chronic inflammation or autoimmune response, leading to uptake by antigen-presenting cells, which present the epitopes to T cells. Upon activation, the T cells, by way of stimulating B cells to become antibody-producing plasma cells, induce autoantibody production, targeting the new antigenic epitopes.

frequent reports of autoimmune blistering diseases occurring in patients who had a long history of psoriasis, a prototype of chronic skin inflammation [2; 8]. Tissue damage resulting from chronic inflammation could release or give access to certain 'previously hidden' target antigens in the skin to antigen-presenting cells, which, upon presenting the target antigen to the T cells, could lead to activation and generation of autoreactive T cells and B cells, followed by the clinical manifestation of autoimmune blistering skin diseases.

Another major mechanism for causing such weakening is genetic mutation. When one or more of these connecting components are formed in a dysfunctional manner, leading to structural weakening, blistering results [5]. Conversely, restoring the expression of these dysfunctional structures by gene correction or by protein delivery results in normal skin structure and function [3; 6]. Several groups of heritable blistering skin diseases in this category include epidermolysis bullosa simplex, junctional epidermolysis bullosa, and epidermolysis bullosa dystrophica, which are caused by mutations in gene-encoding plectin/keratins 5 & 14, laminin-5/BP180/α6β4 integrin, and type-VII collagen, respectively. The third major mechanism for inducing such weakening is toxin from infectious organisms. When these connecting components are directly attacked by these toxins, resulting in structural weakening, blisters surface. One of the best-known examples, bullous impetigo, and its generalized form, staphylococcal scalded-skin syndrome, have recently been determined to be the direct result of enzymatic cleavage of desmoglein 1 by the actions of staphylococcal exfoliative toxins A & B [4].

Other mechanisms that can lead to skin structural weakening include inflammation of a non-autoimmune nature, and metabolic dysregulation. The direct causes of blister formation by the inflammatory and metabolic mechanisms are not as well defined. One possible mechanism for inflammatory blister formation could be due to the proteolytic enzymes released by the infiltrating inflammatory cells. A possible mechanism for metabolic blister formation could be due to the accumulation of toxins in the skin from the metabolic abnormality.

CLASSIFICATION OF DISEASES

Blistering skin diseases can be classified in many different ways. For the purpose of simplicity and easy comprehension, this book classifies them according to disease-causing mechanisms as we currently understand them. One major group of diseases is mediated by autoimmunity and therefore is classified as autoimmune blistering skin diseases. This group is further subclassified by blister location into intraepidermal subgroup and subepidermal subgroup, subdivided by the histological findings of blister formation within the epidermis and underneath the epidermis, respectively. Another major group of diseases is known to be caused by genetic mutation and thus is categorized as heritable blistering skin diseases. The heritable blistering disease group is similarly subcategorized according to the histological (ultrastructural, to be specific) location of the blister: intraepidermal; suprabasal intraepidermal; lamina lucida subepidermal; and sublamina densa subepidermal. The remaining groups of diseases do not fall into either one of the aforementioned categories and are classified as infection-related blistering skin diseases, inflammation-related blistering skin diseases, and metabolic blistering skin diseases. In addition, this book includes a separate section on idiopathic 'palmar plantar pustular dermatoses,' a group of diseases which are considered to be blistering diseases by some, but not all, experts in the field. Finally, the last chapter (Chapter 9) deals with a group of partially characterized blistering dermatoses, for which I hope their presence in this book will help raise physician awareness, thereby facilitating further delineation of these disease entities. Although not perfect, this method of classification results in a logical and intuitively clear organization and hopefully will be helpful for the reader to navigate through the difficult task of making a correct diagnosis, on which, of course, proper treatment is based. A summary of this classification is illustrated in *Table 1*.

TABLE 1 CLASSIFICATION OF DISEASES

Autoimmune	Intraepidermal	Pemphigus vulgaris
		Pemphigus vegetans
		Pemphigus foliaceus
		Pemphigus erythematosus
		Pemphigus herpetiformis
		IgA-mediated pemphigus
		Paraneoplastic pemphigus
	Subepidermal	Bullous pemphigoid
		Lichen planus pemphigoides
		Pemphigoid vegetans
		Pemphigoid nodularis
		Pemphigoid gestationis
		Mucous membrane pemphigoid
		Linear IgA bullous dermatosis
		Chronic bullous dermatosis of childhood
		Epidermolysis bullosa acquisita
		Bullous systemic lupus erythematosus
Heritable	Intraepidermal	Familial benign pemphigus
		Incontinentia pigmenti
	Suprabasal	Epidermolysis bullosa simplex (four variants)
	Lamina lucida	Junctional epidermolysis bullosa (three variants)
	Sublamina densa	Epidermolysis bullosa dystrophica (two forms)
Inflammatory		Dermatitis herpetiformis
		Erythema multiforme (three variants)
		Dyshidrosis
		Allergic contact dermatitis
		Subcorneal pustular dermatosis
		Bullous eruption of insect bites
		Erythema toxicum neonatorum
Metabolic		Porphyria cutanea tarda
		Bullosis diabeticorum
Infectious		Bullous impetigo/Staphylococcal scalded-skin syndrome
		Herpes simplex
		Herpes zoster
		Hand–foot–mouth disease
		Bullous congenital syphilis
		Bullous dermatophyte infections
Pustular		Infantile acropustulosis
		Palmoplantar pustulosis
Partially characterized		Anti-p105 pemphigoid
		Anti-p200 pemphigoid

STRATEGIES FOR DIAGNOSING DISEASES

The best strategy for making an accurate diagnosis of blistering skin diseases is to follow a consistent pathway of evaluation, starting with a thorough clinical examination, including the examinations of the skin, mucous membranes, and nails. In a major project for the development of a widely accepted and comprehensive dermatology terminology to support research, medical informatics, and clinical care in the present and the future, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) of the National Institutes of Health has funded a 'Dermatology Lexicon Project' which was initiated in November 2001 under the contract no. N01-AR-1-2255. Within the scope of this project, a comprehensive list of morphological terminology was established, including the following:

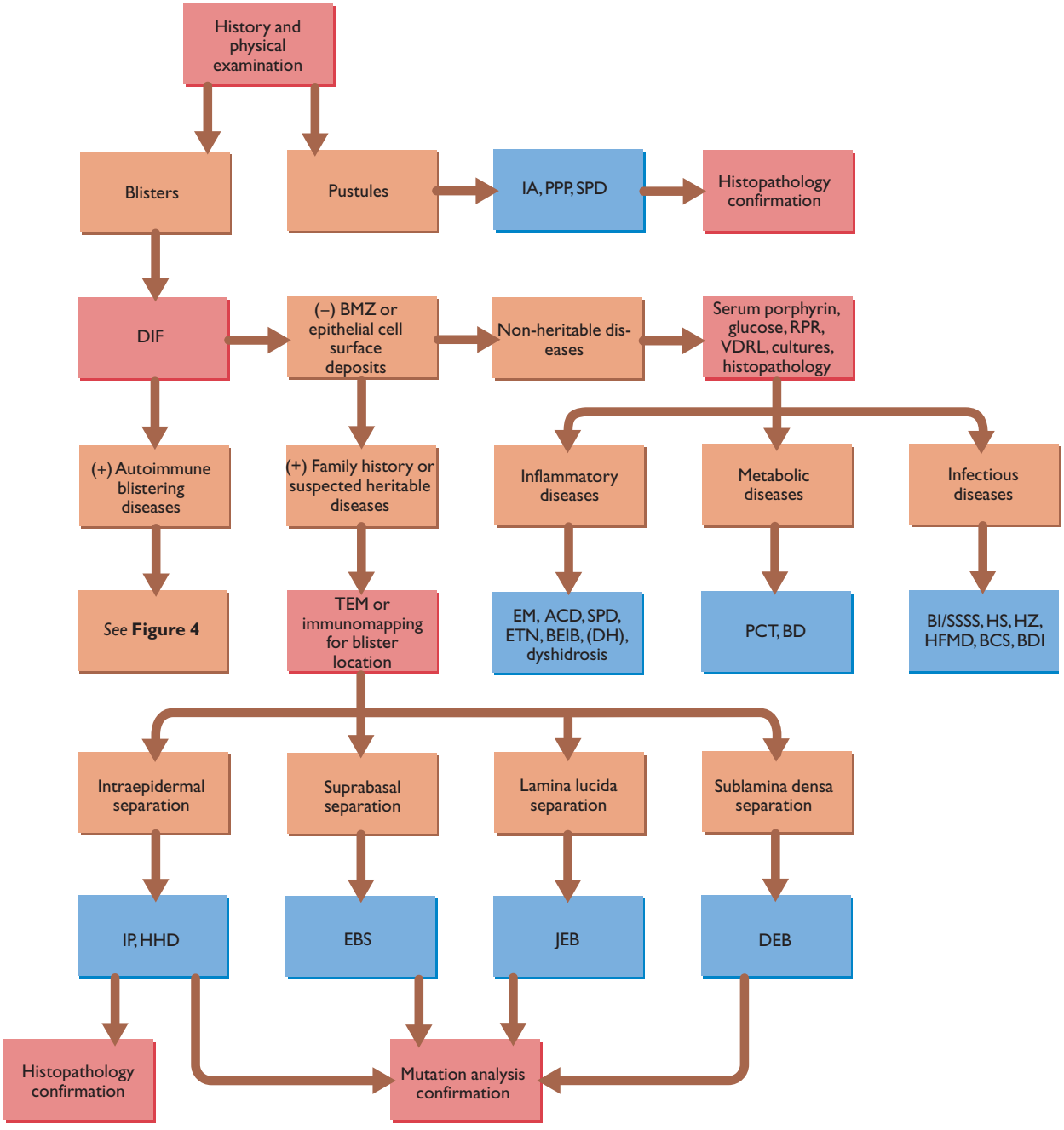
- **Primary lesions:** vesicle vs bulla
- **Secondary features:** crusting, scales, scars, etc.
- **Individual lesions:** annular, serpiginous, etc.
- **Multiple lesion arrangements:** grouped, herpetiform, etc.
- **Distributions:** dermatomal, lymphangitic, etc.
- **Locations:** malar, intertriginous, extensor surface, etc.
- **Signs:** Darier's, Nikolskiy, etc.
- **Textures and patterns:** peau d'orange, etc.
- **Consistency:** soft, firm, hard, tense, flaccid, etc.
- **Color of lesion:** salmon, lilac, blue, etc.
- **Color of body:** jaundice, pallor, rubor, etc.

This list is used throughout this book. Once a thorough clinical examination has been carried out, clinicians should have a better idea as to proper categorization.

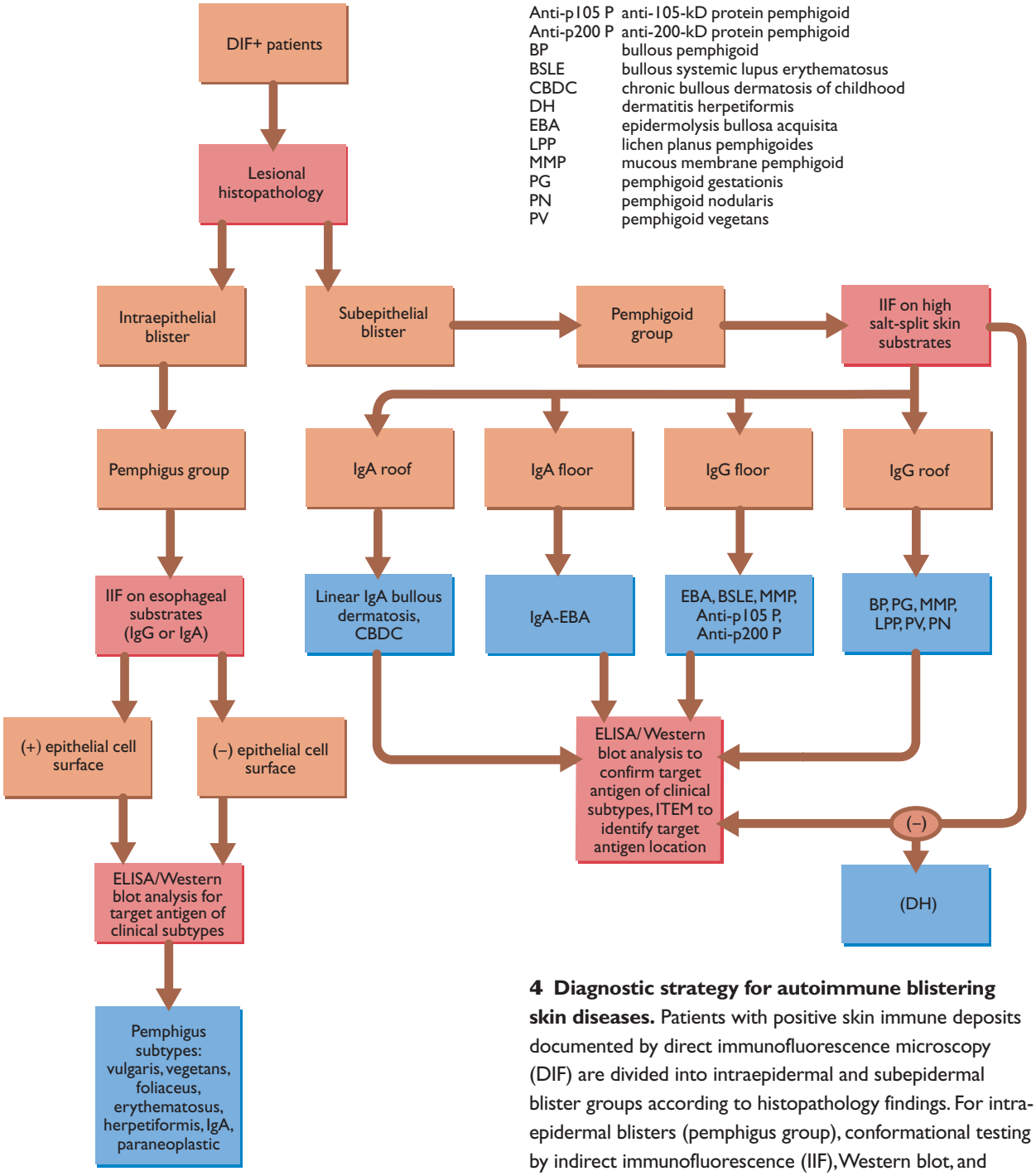
Besides clinical evaluation, assigning final diagnosis of blistering skin diseases requires certain confirmative diagnostic laboratory tests. There are three major reasons for the use of laboratory tests, in addition to a thorough clinical examination. Firstly, clinical manifestations of a given disease vary from patient to patient. Secondly, clinical manifestations of two distinct disease entities can share similar features. (These first two reasons are evident in the subsequent sections of clinical diseases.) Thirdly, establishing an accurate clinical diagnosis, well documented by laboratory tests, is good medical practice before patients are subjected to various immunosuppressive treatments that involve potentially serious side effects.

3 Diagnostic strategy for non-autoimmune blistering skin diseases. Starting with history and physical examination, blistering diseases that are shown to be immune-deposit negative by direct immunofluorescence microscopy (DIF) are considered to be non-autoimmune. Divided into heritable and non-heritable groups, the heritable non-autoimmune blistering diseases should be characterized further by transmission electron microscopy and/or immunomapping, whereas the non-heritable, non-autoimmune blistering diseases should be characterized further by histopathology and serological tests for porphyrin (to rule out porphyria cutanea tarda), glucose (to rule out bullosis diabeticorum), rapid plasma reagin, venereal disease research laboratory (to rule out bullous congenital syphilis), and bacterial and viral culture (to rule out bullous impetigo, herpes simplex, herpes zoster, and hand–foot–mouth disease). (Note that although positive DIF findings are present in DH, it is generally considered to be a non-autoimmune blister.)

For patients with suspected autoimmune blistering skin diseases, routine histopathology as well as direct and indirect immunofluorescence microscopy examinations are recommended for all patients [10]. In certain circumstances, additional tests, such as immunoblotting, immunoprecipitation, ELISA, and immunotransmission electron microscopy, as illustrated in the subsequent sections, may be required to secure an accurate diagnosis [10; 14; 16]. For patients with suspected heritable blistering skin diseases, routine histopathology has little value in determining the final diagnosis and is therefore not commonly used, unless other non-heritable blistering skin diseases are also under consideration; instead, transmission electron microscopy and/or immunomapping should be utilized for delineating the final diagnosis [12; 17]. In addition, gene-mutation analysis should be performed for the purpose of assisting genetic counseling. For patients with infection-related blistering skin diseases, routine histopathology examination should be carried out. In certain circumstances, culturing the suspected microorganism should be performed as well. For inflammation-related and metabolic blistering skin diseases, direct immunofluorescence microscopy is helpful, in addition to the routine histopathology examination [9; 13]. The diagnostic strategy for non-autoimmune blistering diseases is shown in Figure 3, while that for autoimmune-mediated diseases



ACD	allergic contact dermatitis
BCS	bullous congenital syphilis
BD	bullosis diabeticorum
BDI	bullous dermatophyte infections
BEIB	bullous eruption of insect bites
BI	bullous impetigo
DEB	dystrophic epidermolysis bullosa
DH	dermatitis herpetiformis
EBS	epidermolysis bullosa simplex
EM	erythema multiforme
ETN	erythema toxicum neonatorum
HFMD	hand–foot–mouth disease
HHD	Hailey–Hailey disease
HS	herpes simplex
HZ	herpes zoster
IA	infantile acropustulosis
JEB	junctional epidermolysis bullosa
IP	incontinentia pigmenti
PCT	porphyria cutanea tarda
PPP	palmoplantar pustulosis
SPD	subcorneal pustular dermatosis
SSSS	Staphylococcal scalded-skin syndrome



Anti-p105 P	anti-105-kD protein pemphigoid
Anti-p200 P	anti-200-kD protein pemphigoid
BP	bullous pemphigoid
BSLE	bullous systemic lupus erythematosus
CBDC	chronic bullous dermatosis of childhood
DH	dermatitis herpetiformis
EBA	epidermolysis bullosa acquisita
LPP	lichen planus pemphigoides
MMP	mucous membrane pemphigoid
PG	pemphigoid gestationis
PN	pemphigoid nodularis
PV	pemphigoid vegetans

4 Diagnostic strategy for autoimmune blistering skin diseases. Patients with positive skin immune deposits documented by direct immunofluorescence microscopy (DIF) are divided into intraepidermal and subepidermal blister groups according to histopathology findings. For intraepidermal blisters (pemphigus group), conformational testing by indirect immunofluorescence (IIF), Western blot, and ELISA helps in achieving a more detailed analysis. For subepidermal blisters (pemphigoid group), IIF performed on high-salt/split skin substrates divides the group into several major subgroups. Additional studies – ELISA, Western blot, and immunoelectron microscopy (ITEM) – facilitate the final determination of specific disease entities. (Note that DH is generally not considered to be an autoimmune disease.)

is shown in **4**. Although positive direct immunofluorescence findings are generally indicative of autoimmune diseases, two blistering diseases with positive direct immunofluorescence findings, namely porphyria cutanea tarda and dermatitis herpetiformis, are categorized under non-autoimmune diseases, due to the lack of data supporting their autoimmune nature. An additional stepwise approach to the diagnosis of blistering diseases is given by Powell and Black [15]. Furthermore, details on the algorithmic approach to subclassification of heritable epidermolysis bullosa groups of diseases are available in the work of Fine *et al* [11].

REFERENCES

Mechanisms of blister formation

[1] Anhalt GJ, Labib RS, Voorhees JJ, Beals TF, Diaz LA. Induction of pemphigus in neonatal mice by passive transfer of IgG from patients with the disease. *N Engl J Med* 1982; **306** (20): 1189–96.

[2] Chan LS, Vanderlugt CJ, Hashimoto T, Nishikawa T, Zone JJ, Black MM, Wojnarowska F, Stevens SR, Chen M, Fairley JA, Woodley DT, Miller SD, Gordon KB. Epitope spreading: lessons from autoimmune skin diseases. *J Invest Dermatol* 1998; **110** (2): 103–9.

[3] Chen M, Kasahara N, Keene DR, Chan L, Hoeffler WK, Finlay D, Barcova M, Cannon PM, Mazurek C, Woodley DT. Restoration of type-VII collagen expression and function in dystrophic epidermolysis bullosa. *Nat Genet* 2002; **32** (4): 670–5.

[4] Hanakawa Y, Schechter NM, Lin C, Garza L, Li H, Yamaguchi T, Fudaba Y, Nishifuji K, Sugai M, Amagai M, Stanley JR. Molecular mechanisms of blister formation in bullous impetigo and staphylococcal scalded skin syndrome. *J Clin Invest* 2002; **110** (1): 3–60.

[5] Heinonen S, Mannikko M, Klement JF, Whitaker-Menezes D, Murphy GF, Uitto J. Target inactivation of the type-VII collagen gene (Col7a1) in mice results in severe blistering phenotype: a model for recessive dystrophic epidermolysis bullosa. *J Cell Sci* 1999; **112** (Pt 21): 3641–8.

[6] Woodley DT, Keene DR, Atha T, Huang Y, Lipman K, Li W, Chen M. Injection of recombinant human type-VII collagen restores collagen function in dystrophic epidermolysis bullosa. *Nat Med* 2004; **10** (7): 693–5.

[7] Yancey KB. The pathophysiology of autoimmune blistering diseases. *J Clin Invest* 2005; **115** (4): 825–8.

[8] Yasuda H, Tomita Y, Shibaki A, Hashimoto T. Two cases of subepidermal blistering disease with anti-p200 or 180-kD bullous pemphigoid antigen associated with psoriasis. *Dermatology* 2004; **209** (2): 149–55.

Strategies for diagnosing diseases

[9] Ash S, Woodley DT, Chan LS. Porphyria cutanea tarda preceding AIDS. *Lancet* 1996; **347** (8995): 190.

[10] Chan LS, Ahmed AR, Anhalt GJ, Bernauer W, Cooper KD, Elder MJ, Fine J-D, Foster CF, Ghohestani R, Hashimoto T, Hoang-Xuan T, Kirtschig G, Korman NJ, Lightman S, Lozada-Nur F, Marinkovich MP, Mondino BJ, Prost-Squarcioni C, Rogers RS III, Setterfield JF, West DP, Wojnarowska F, Woodley DT, Yancey KB, Zillikens D, Zone JJ. The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. *Arch Dermatol* 2002; **138** (3): 370–9.

[11] Fine J-D, Eady RA, Bauer EA, Briggaman RA, Bruckner-Tuderman L, Christiano A, Heagerty A, Hintner H, Jonkman ME, McGrath J, McGuire J, Moshell A, Shimizu H, Tadini G, Uitto J. Revised classification system for inherited epidermolysis bullosa: report of the second international consensus meeting on diagnosis and classification of epidermolysis bullosa. *J Am Acad Dermatol* 2000; **42** (6): 1051–66.

[12] Hintner H, Stingl G, Schuler G, Fritsch P, Stanley J, Katz S, Wolff K. Immunofluorescence mapping of antigenic determinants within the dermal–epidermal junction in the mechanobullous diseases. *J Invest Dermatol* 1981; **76** (2): 113–18.

[13] Katz SI, Hall RP III, Lawley TJ, Strober W. Dermatitis herpetiformis: the skin and the gut. *Ann Intern Med* 1980; **93** (6): 857–74.

[14] McMillan JR, Matsumura T, Hashimoto T, Schumann H, Bruckner-Tuderman L, Shimizu H. Immunomapping of EBA sera to multiple epitopes on collagen VII: further evidence that anchoring fibrils originate and terminate in the lamina densa. *Exp Dermatol* 2003; **12** (3): 261–7.

[15] Powell AM, Black M. A stepwise approach to the diagnosis of blisters in the clinic (1). *Clin Dermatol* 2001; **19** (5): 598–606.

[16] Shimizu H, Masunaga T, Ishiko A, Matsumura K, Hashimoto T, Nishikawa T, Domlege-Hultsch N, Lazarova Z, Yancey KB. Autoantibodies from patients with cicatricial pemphigoid target different sites in epidermal basement membrane. *J Invest Dermatol* 1995; **104** (3): 370–3.

[17] Smith LT. Ultrastructural findings in epidermolysis bullosa. *Arch Dermatol* 1993; **129** (12): 1578–84.

CHAPTER TWO

Diagnostic methods

METHODS OF SKIN BIOPSY

Skin biopsy performed for the purpose of diagnosing blistering skin disease is an essential component of proper disease management. Depending on the purpose of a given biopsy, it can be obtained from lesional skin or from perilesional skin. In addition, the skin samples collected are placed in a different preserving medium or compound according to the type of tests for which they will be used. Careful consideration of the biopsy location and the preserving medium ensures the most efficient way of obtaining an accurate diagnosis.

BIOPSY FOR ROUTINE HISTOPATHOLOGY

A 4-mm-size punch biopsy is usually sufficient for routine histopathology. Biopsy should be performed, if possible, on a fresh lesion, *i.e.*, a blister that has been surfaced within the previous 24 hr. The epidermis of a blister, whether it is intraepidermal or subepidermal in nature, has been separated from within, or from, the underlying dermis, at least partially; therefore, a portion of intact skin should be included in the biopsy specimen, so that the epidermis will not be detached from the rest of the biopsy. The biopsy obtained should be placed in 10% formaldehyde (formalin) solution immediately for further processing. Some experts in the field, however, prefer to obtain a skin biopsy from a small blister by an elliptical method to ensure that the entire blister is present in the biopsy. The advantages of an elliptical biopsy are that the blister roof is unlikely to be detached from the biopsy process, and that an accurate diagnosis can be ensured from the biopsy.

BIOPSY FOR DIRECT IMMUNOFLUORESCENCE MICROSCOPY

A 4-mm-size punch biopsy is usually sufficient for direct immunofluorescence microscopy. Because lesional skin usually contains inflammatory cells and substances, the presence of which could destroy the immune deposits, obtaining a lesional skin sample for direct immunofluorescence microscopy may result in a falsely negative finding in a patient with positive immune-mediated skin disease; thus, a perilesional skin sample is usually obtained for this test, in order to avoid false-negative results. The perilesional skin sample should be placed in a liquid-turned-solid compound called optimal cutting temperature (OCT) compound and frozen immediately at –20°C and stored at –80°C until processing. The OCT compound is commercially available at Ted Pella, Inc. (Redding, Calif.; www.tedpella.com) or GTI Microsystems (Tempe, Ariz; www.gtimicrosystems.com). Alternatively, the skin sample can be placed in normal saline-soaked gauze and kept at 4°C. (The sample should be frozen in OCT compound within the subsequent few hours.) Another way of preserving the skin sample is Michel's medium, which preserves skin samples at room temperature for approximately 6 months [3]. Michel's medium-preserved skin samples should be washed thoroughly to reduce background staining before being processed for direct immunofluorescence microscopy.