AN ATLAS OF SKIN BIOPSY

Diagnosis by Light and Immuno Microscopy of Vesico-Bullous, Connective Tissue Disorders and Vasculitis of the Skin

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This bench reference will well serve all who are interested in dermatopathology: pathologists, dermatologists, residents and students. The authors concentrate on immunodermatopathology, illustrating the light and immunofluorescent patterns of cutaneous vasculitis and commonly encountered vesico-bullous and connective tissue skin diseases. The format encompasses concise clinical facts, histology and immunology. All photographs are of routinely prepared sections and, in most cases, the light microscopic and immunofluorescent studies were done on the same specimen. Following the text and references, appendices provide notes on abbreviations and illustrations, biopsy procedure and tissue handling, patterns in certain skin diseases, and self-assessment.

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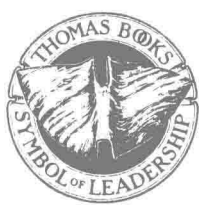

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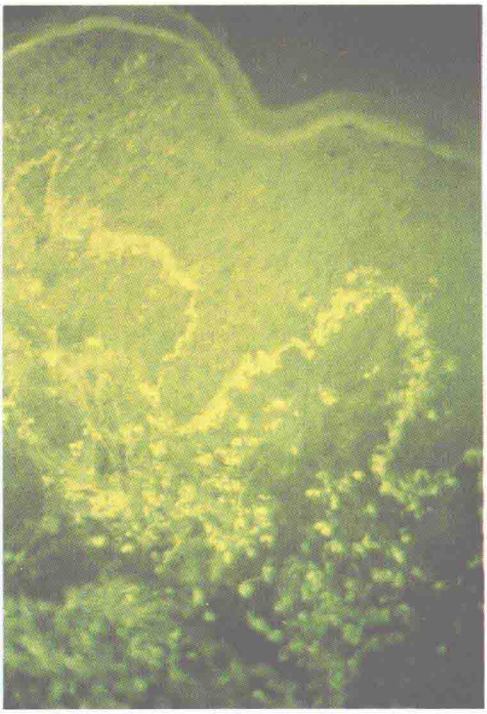
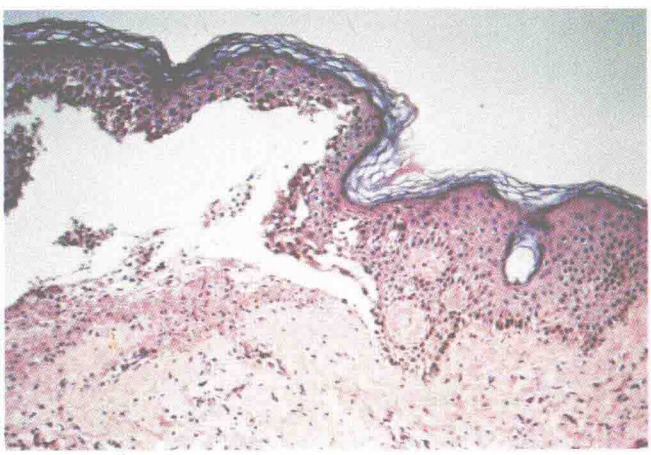


Bullous pemphigoid
Immuno-microscopic appearance



Light microscopic appearance

TO OUR WIVES AND CHILDREN

PREFACE

THIS atlas is intended for use as a bench reference by general pathologists interested in dermatopathology, residents and senior medical students, and those who wish to be more familiar with the recent advances in immuno-dermatopathology. Our objective is to illustrate the light and immunofluorescence patterns of commonly encountered vesico-bullous and connective tissue diseases of the skin. We have selected cases wherein we have found combined light and immunofluorescent microscopy quite helpful in arriving at a correct diagnosis and have left out areas of current controversies for future resolution. A section in the Appendix also deals with tissue handling procedures.

All photographs have been taken of routinely prepared tissue sections. We have used hematoxylin and eosin stained sections for light microscopic illustrations. Magnifications are given with each figure. The immunofluorescence photographs were originally taken on Ektachrome 200® films and then were reproduced as black and white prints for this atlas. In most of our case illustrations, the light microscopic and immunofluorescence studies were done on the same biopsy specimens. One-half was used for light microscopy while the other half was used for immunofluorescence studies. The format used will provide the readers with practical and theoretical bases of diseases discussed and guide them to improve their proficiency and skill. Test questions at the end of the book will be helpful in evaluating comprehension of the subject matter. Selected references will lead the inquisitive mind to seek out further details. In this manner, the atlas will enhance the self education process.

We offer our sincere thanks to Dr. Albert G. Smith for his continued interest and support. We are most grateful to our clinical colleagues Dr. Paul R. Winder and his staff of the Dermatology service for supplying biopsy materials from which these illustrations were taken. We also acknowledge the skillful technical help of Ms. Caron M. Gross and other histo-technologists of our laboratories for processing and staining the tissue sections. To our publisher, Mr. Payne Thomas, we express our sincere appreciation for his encouragement, cooperation, and persistence during the preparation of

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AN ATLAS OF SKIN BIOPSY

BIOPSY OF SKIN

ACCURATE diagnosis is the first requisite for institution of appropriate therapy. Skin as an organ offers an unusual opportunity, due to its accessibility, to study the biopsy materials by histo- and immunopathologic means. This is particularly useful in cases of chronic bullous dermatoses and autoimmune connective tissue disorders involving the skin. In this vein, removal of an adequate and well-selected biopsy specimen of skin is of utmost importance. Single or multiple specimens may be required to come to a definitive diagnosis, and thus they should be taken. Biopsy procedure usually produces only minor discomfort to the patient, but in difficult cases, the benefits derived are immense. For best results, close cooperation and consultation between the clinician and pathologist are imperative. It must be stressed that histo- and immunopathology are only complementary to clinical dermatology and to other pertinent laboratory tests. In a large percentage of cases, a biopsy specimen will disclose convincing diagnostic features.

Proper handling of biopsy specimen is also important. A poorly selected, inadequate, and badly handled biopsy specimen may lead to erroneous diagnostic interpretations. Properly performed biopsy with meticulous care and handling of tissue may protect the patient from unnecessary expenses and morbidity. The following guiding principles adapted and expanded from Beerman should apply in selecting proper biopsy specimens:

1. Avoid traumatized or otherwise injured lesions, particularly with secondary changes, or those modified by treatment.
2. A fully developed lesion is preferable, although multiple biopsies at various stages of evolution may be more helpful.
3. Avoid "burned out" or scarred lesions, except for where specifically indicated.
4. The biopsy should include both the lesion and a portion of adjacent uninvolved skin.

Although there are no increased risks and dangers in taking a skin biopsy, infections and scar formation may occur in susceptible persons and locations.

Hence, proper evaluation and precautions must be taken prior to the biopsy procedure.

Since taking a biopsy in a living patient is an important step towards the establishment of a correct diagnosis, Beerman has suggested that biopsy "deserves all the meticulous care and thoroughness that are accorded to a necropsy, for it is even more important to reach a correct diagnosis in a living patient than to establish it postmortem."

PEMPHIGUS VULGARIS

Clinical manifestations

PEMPHIGUS vulgaris (PV) is characterized by flaccid bullae arising on normal appearing skin or mucous membrane. These bullae break easily, leave weeping denuded areas, and display little tendency to heal. If downward pressure is applied to a blister, it extends peripherally (blister-spread phenomenon of Asboe-Hansen). If friction is exerted on apparently normal skin, the epidermis may be removed leaving a moist red denuded surface (Nikolsky sign). It occurs most commonly in the forty to sixty year age group but has been observed in all ages, including children. It happens in all races and has a predilection for Jews and other Mediterranean ethnic groups. Extensive oral lesions are usually present and often are the first manifestation of the disease. The isolated lesions may persist for a long time before becoming generalized. There is some positive association between PV and HLA-A10 and HLA-B13 phenotypes and other autoimmune diseases like SLE, myasthenia gravis, and thymoma.

Histologic features

See Figure 1.

1. Eosinophilic spongiosis is often the earliest change.
2. Acantholysis with formation of suprabasal clefts and bullae.
3. Bulla cavity contains acantholytic and degenerating keratinocytes.
4. Acantholysis usually involves adnexal structures.
5. Basal cells remain attached to the dermis like a "row of tombstones."
6. Papillomatosis and villi formation.
7. The dermis contains varying numbers of a mixed inflammatory-cell infiltrate.

Histologic differential diagnosis

1. Familial benign chronic pemphigus (Hailey and Hailey disease):
   – more extensive acantholysis usually involving the entire epidermis giving it the appearance of a delapidated brick wall.

– acantholysis does not involve adnexal structures.
– the epidermis tends to become more hyperplastic.

2. Darier's disease:
   – less acantholysis with smaller clefts and lacunae formation.
   – prominent dyskeratosis with formation of corps ronds and grains.
   – focal vertical columns of parakeratosis.
3. Viral vesicles:
   – ballooning and reticular degeneration of the epidermis.
   – multinuclear giant cells and inclusion bodies.
4. Actinic keratosis with acantholysis:
   – nuclear atypia of keratinocytes.
   – solar elastosis of upper dermis.
5. Pemphigus vegetans: intraepidermal abscesses containing mainly eosinophils.
6. Pemphigus foliaceus and pemphigus erythematosus: acantholysis mainly in the upper part of the epidermis.

COMMENT: Histologic differentiation of pemphigus vulgaris from Hailey and Hailey disease and other intraepidermal acantholytic diseases is not always possible. Differentiation may be accomplished by immunofluorescent studies.

Immunofluorescence

See Figure 2.

1. DIF shows predominantly granular deposits of IgG, and occasionally of IgM or IgA, and C_3 in the intercellular spaces of lesional and perilesional skin.
2. Similar deposits may also be present in normal skin of pemphigus patients, twenty-four hours post radiation with phototoxic doses of (spectrum B) ultraviolet light.
3. Above patterns are seen in all types of pemphigus except for the extent and sites of localization.
4. Biopsies of bullae yield erroneous results due to secondary changes.

COMMENT: IF pattern may be critical in differentiating pemphigus from erythema annulare centrifugum, acantholytic dermatitis, Hailey and Hailey disease, aphthous ulcer, EM, etc. In these diseases, DIF findings reveal negative reactions. In pemphigus erythematosus, deposits of IgG at the D/E junction may also be present in the biopsies taken from sun-exposed areas. This finding is less frequent if the biopsy is taken from the trunk and non-sun-exposed areas. Intercellular deposits, like pemphigus, also have been shown to occur in pyoderma vegetans, thermal burns, pemphigoid, fungal infection, leprosy, and in patients treated with penicillamine. Peripheral nuclear patterns, as in LE, may resemble the intercellular pattern of pemphigus.

Immunopathology

Pemphigus was the first dermatologic disease in which participation of autoimmune mechanism was demonstrated. It is the most serious chronic bullous disease of skin and mucous membranes. It is characterized by acantholysis due to the presence of auto-antibodies directed against intercellular cement substances of squamous epithelium. The exact nature of the intercellular antigen is unknown. It is a saline soluble glycoprotein of approximately 68,000 molecular weight. Since the antibodies bind to the glycocalyx coats of epidermal cells, this substance may be the source of pemphigus antigen. The antibody is usually of the IgG subclass. The exact role of the antibody in the pathogenesis is not yet fully defined. It is thought that the acantholysis may be the result of complement fixation at the intercellular zone by the pemphigus antibody via the classic pathway. Secondary changes in keratinocytes, like inhibition of RNA for protein synthesis, may sustain this acantholysis. The other view suggests that binding of pemphigus antibody to the epithelial cell receptors may block them or stimulate them to secrete proteases that alter the intercellular cement substances. Altered cement substances can no longer hold epidermal cells together, thus leading to acantholysis.

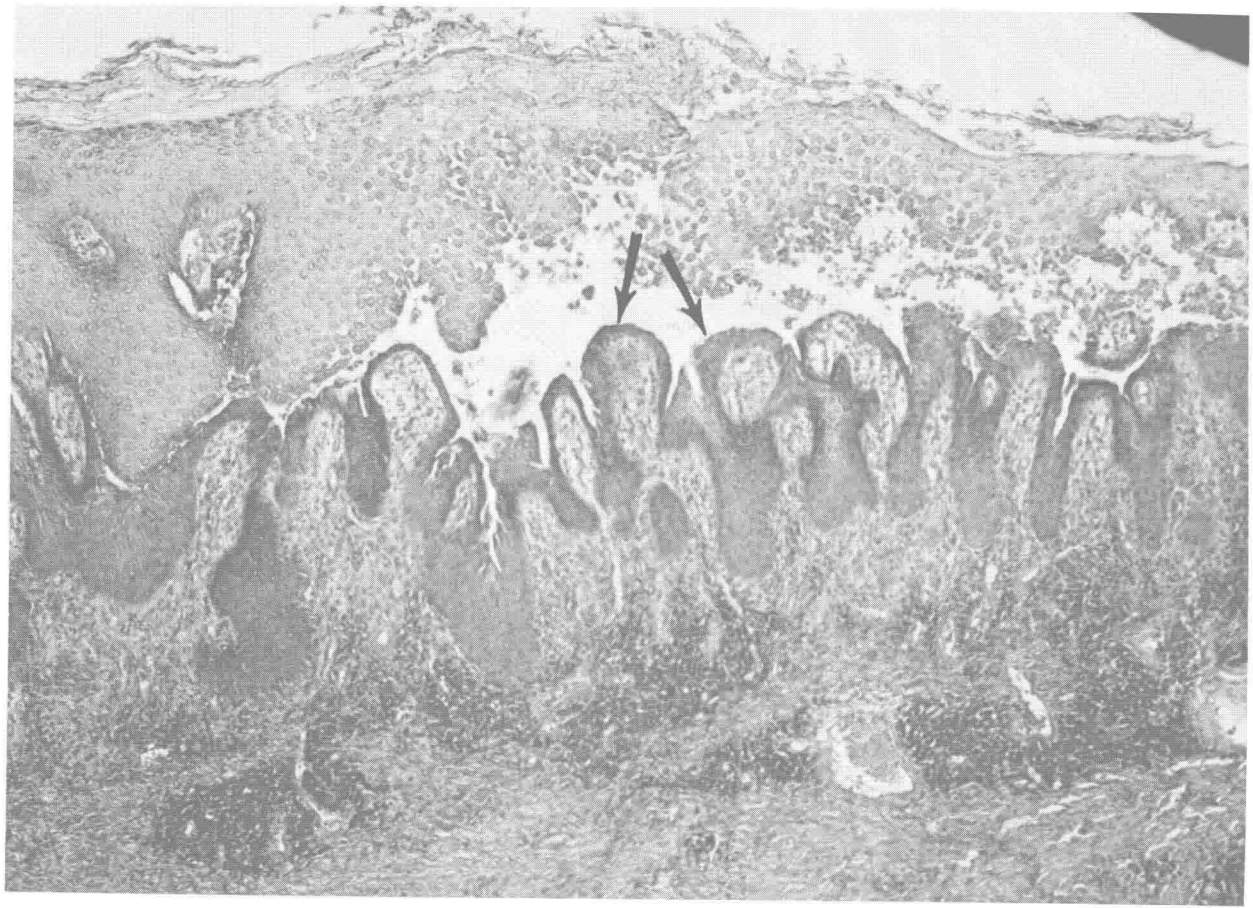

Figure 1. Pemphigus vulgaris. There is an intraepidermal, predominantly suprabasal blister containing acantholytic keratinocytes. Papillomatosis is seen lined by a layer of basal cells, so-called villi (arrows). Magnification X40.