[James H. Herndon]

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Blistering Diseases
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Case 1: Pemphigus Vulgaris

[redacted] a 53 year old [redacted] woman was admitted on [redacted], 1963 after a two-week history of sore throat. Small painful ulcers developed in her mouth, then a blister was noted on the forehead. This soon ruptured and drained fluid continually, showing no tendency to heal. Blisters appeared on the trunk and quickly became shallow erosions. Three days before admission lesions appeared in the vagina and vulva.

On initial examination many shallow erosions were noted on the pharynx and posterior palate. The tongue showed several ulcers. The trunk was covered with small, irregular tense flaccid bullae, but her arms and legs were spared.

Her laboratory studies were unremarkable. She felt well and remained afebrile. A skin biopsy showed pemphigus vulgaris. She was started on 80 mg prednisone a day and was discharged after five days to be followed in clinic. At the time of discharge she had improved very little and was apparently getting new lesions.

Two weeks after discharge she was seen in clinic and seemed to be clearing slowly. However, she had been given an "A" card and found herself unable to pay for further visits or for medication. About ten days after her clinic visit she ran out of prednisone. A few days later new blisters began appearing and old erosions that had been healing under their crusts became raw and painful again.

On [redacted] 1963, a little over a month following discharge and approximately six weeks after the start of her illness she presented to the emergency room with massive involvement. Most of the trunk was denuded with generalized purulent oozing. Now her face and extremities showed many small and medium sized bullae, though her mouth and lower legs were clear.

Prednisone was restarted at 80 mg daily but eight days later the skin had worsened and the dose was increased by 4 tablets daily to 100 mg. Five days later on day 13 it was raised to 150, on day 20 to 200, on day 24 to 250, and finally on day 27 500 mg of prednisone was given. The patients condition never improved but inexorably worsened. After developing repeated staph and gram negative septicemia, anemia, and azotemia she died on the 30th hospital day.

Case 2: Pemphigus Foliaceus

[redacted] a 61 year old [redacted] man was seen in the Dermatology clinic on [redacted], 1969 with a one-year history of a vesicular eruption beginning on the face, back and chest. The process spread very slowly. Ruptured vesicles left scaling and crusting lesions behind. Itching was quite severe, though none of the eruption was painful. There were no mouth lesions.

Examination showed a muscular, well appearing man with a confluent, scaling, and crusting eruption on the upper trunk and neck. Hyperpigmentation was prominant in the affected areas and only a few vesicles could be seen at the margins of the lesions. These could be dislodged along with nearby normal appearing skin by sliding finger pressure. A biopsy showed pemphigus foliaceus, and the patient was begun on prednisone.

Initially 75 mg daily was required to prevent new lesions from appearing. Within two months he had developed florid diabetes mellitus unresponsive to oral anti-diabetic agents and was admitted to the hospital. Congestive heart failure developed after discharge, apparently on an atherosclerotic basis, and the patient became severely depressed, refusing to eat. Although cyclophosphamide was started during his second admission the patient was lost to followup on discharge on [redacted] 1969. At that time his eruption was controlled with 40 mg prednisone every other day, 150 mg cyclophosphamide daily. Digitalis and diuretics were required for control of the congestive state, but anti-diabetic agents ceased to be required at the lower prednisone dose.

Case 3: Bullous Pemphigoid

[redacted] a 74 year old [redacted] male was admitted [redacted] 1970 after a seven month history of bullous skin disease beginning on one foot. It had spread rapidly to involve most of the flexural surfaces and the anterior trunk. The blisters contained clear fluid, lasted several days before rupturing, and showed a good tendency to heal. He had no mouth lesions. Prednisone 20 mg daily controlled the eruption well enough for him to continue in his watch repair business, but he relapsed whenever the drug was stopped. Back pain present before his illness started, rapidly worsened, and he was hospitalized because of steroid exacerbated osteoporosis and his bullous disease, which had been called pemphigus vulgaris.

Examination showed a thin, elderly man who could not move without back pain. A large ulcer occupied the left lower leg, but only a few semi-collapsed bullae were noted, mostly on his thighs and trunk. He had a few non-tender shallow gingival erosions. His laboratory findings were unremarkable save for a low albumin. The skin biopsy showed a subepidermal bulla, and his serum was found to contain antibodies that fixed to the basement zone of normal human skin in vitro. He was discharged on prednisone 40 mg, cyclophosphamide 100 mg and local measures for the ulcer, which appeared to be healing well.

After discharge the cyclophosphamide dose was reduced to 50 mg daily because of modest leucopenia, and the prednisone tapered slowly. New bullae developed after he omitted the prednisone a few weeks after discharge and on [redacted] 1970 he was readmitted with intercurrent bronchopneumonia.

Physical examination showed only a few healing erosions on the skin surface and signs of right lower lobe bronchopneumonia. Penicillin was given though no pathogens could be isolated from sputum. An upper gi series done because of persistant complaints of dysphagia showed a small gastric ulcer. He left the hospital in two weeks on prednisone 75 mg daily with maalox, but not on cyclophosphamide.

On [redacted] 1970 he died, having perforated the gastric ulcer.

Case 4: Dermatitis Herpetiformis

[redacted] a 54 year old [redacted] man was seen in the Dermatology clinic on [redacted] 1970 for an extremely pruritic eruption on elbows and sacrum which had been present for three weeks. On further questioning he recalled frequent relapses and remissions since 1945, never treated with systemically administered medication.

Examination showed a well appearing man with clusters of erythematous papules and 1 or 2 small vesicles on an erythematous base. The elbows, scapulae, and sacral areas showed mild punctate scars and hyperpigmentation suggesting long-term disease.

Diasone 2-3 tabs daily has kept his eruption completely suppressed since then.

Bullous Disorders: Historical Outline (1)

c.400 BC — Hippocrates mentioned pemphigoid fever (pemphigodes pyretoi) but did not describe.

c.200 AD — Galen described febris pemphigodes, a fever associated with pustules in the mouth. Pemphix (genitive pemphigos) is the Greek root meaning bubble, and some have speculated that both Galen and Hippocrates were referring to herpes labialis.

before 1750 — Several authors applied the term pemphigus to disorders that may have represented, in addition to herpes simplex, bullous impetigo, contact dermatitis, or erythema multiforme.

1791 — First case of probable true pemphigus described under that name by Wichmann (Erfurt).

1844 — Cazenave (Paris) recognized pemphigus foliaceus as a distinct but related disorder.

1884 — Duhring (Philadelphia) described dermatitis herpetiformis (2).

1886 — Neumann (Vienna) delineated pemphigus vegetans as a variant of pemphigus.

1895 — Nikolsky (Kiev) in his published thesis described a characteristic sign of Cazenave's pemphigus foliaceus (3).

1911 — Thost (Heidelberg) distinguished a non-fatal bullous, scarring disease of mucous membranes. He applied the name benign mucosal pemphigus. Lever later renamed it benign mucosal pemphigoid when the sub-epidermal location of the bulla was recognized.

1926 — Senear and Usher (Chicago) described a disorder they considered a hybrid of pemphigus and lupus erythematosus (4). Ormsby applied the name pemphigus erythematosus a few years later.

1943 — Civatte (Paris) first published the critically important observation that in pemphigus vulgaris, bullae form within the epidermis by loss of intercellular cohesiveness and disappearance of desmosomal attachments (a process called acantholysis).

1948 — Tzanck (Paris) described a rapid cytodiagnostic test permitting simple identification of acantholytic cells specific for pemphigus vulgaris.

1951 — Using Civatte's (Paris) contribution in reviewing the collected experience at the Massachusetts General Hospital, Lever separated for the first time a group of patients with strictly subepidermal bullae from those having the intraepidermal acantholytic cleavage characteristic of pemphigus vulgaris (5). At first he labelled the group with subepidermal blisters chronic pemphigus vulgaris since they lived far longer, but in

1953 — Lever (Boston) published his great review in Medicine (6), setting out clearly the clinical and pathologic features of all the major acquired bullous diseases. In this work he established bullous pemphigoid as the term for the chronic, relatively benign subepidermal blistering disease without acantholysis. This group contained some patients whose previous diagnosis was pemphigus and some thought to have Duhring's dermatitis herpetiformis.

Historical Outline, cont'd.

1956 Sneddon and Wilkinson (Sheffield) further separated subcorneal pustular dermatosis from the large and various category of dermatitis herpetiformis (8).

1956 Characterized simultaneously in South Africa (Lang and Walker 9) and Scotland (Lyell 10), Toxic Epidermal Necrolysis has since been reported from all parts of the world.

1964 In studies begun while a medical student at Buffalo, Robert Jordan (at the initial suggestion of his father James Jordan and in collaboration with Ernst Beutner) made the arresting discovery that serum from most patients with pemphigus vulgaris contains antibodies directed against intercellular substance of stratified squamous epithelium (11). This finding opened a completely new area of immunologic investigation in skin diseases, and led to improved diagnostic methods and the exciting prospect of understanding the pathogenesis of and applying rational therapy to this group of disorders.

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I. Pathophysiology of Blister Formation

A. Basis for cellular adhesion in skin.

1. Dermoepidermal junction.

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2. Intercellular cohesiveness within the epidermis.

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BULLOUS ERUPTIONS: Age and Frequency (modified from 66)

	Common	Unusual
Infancy	Impetigo	Epidermolytic Hyperkeratosis Erythropoietic Porphyria Congenital Syphilis Epidermolysis Bullosa Urticaria Pigmentosa Incontinentia Pigmenti Toxic Epidermal Necrolysis Juvenile Pemphigoid Acrodermatitis Enteropathica
Childhood	Impetigo Bullous Reaction To Insect Bites Erythema Multiforme	Bullous Drug Eruptions
Adult	Bullous Reaction To Insect Bites Erythema Multiforme Bullous Drug Eruptions Contact Dermatitis	Morphea Lichen Sclerosis et Atrophicus Dermatitis Herpetiformis Herpes Gestationis Benign Familial Pemphigus Pemphigus Vulgaris, Foliaceus Photosensitive Porphyria Bullae Associated with Unconscious States
ld Age	Bullous Pemphigoid	Benign Mucosal Pemphigoid

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B. Possible mechanisms of dermo-epidermal separation.

1. By disintegration of basal cells.

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VESICLES AND BULLAE: Classification Based on Morphology (modified from 66)

Site or Description	Entity	Mode of Formation
Subcorneal	Impetigo	infection
	Subcorneal pustular dermatosis	unknown
	Staphylococcal Toxic Epidermal Necrolysis	exotoxin
	Pemphigus Foliaceus/Erythematosus	acantholysis
	Miliaria crystallina	sweat duct occlusion
Upper Epidermis	Epidermolytic Hyperkeratosis	granular degeneration
Mid Epidermis; Spongiosis	Dermatitis-eczema group (including photoallergic)	lymphotoxins?
	Incontinentia Pigmenti	unknown
	Viral Infections (Vaccinia, Variola, Varicella-Zoster, Herpes Simplex)	cytotoxicity
	Fungal Infections including Candida	mixed
	Pityriasis Rosea	unknown
	Pustular Psoriasis	unknown
Mid Epidermis; Primary Cell Injury	Ionizing Radiation (UV, Xray)	complex primary damage
	Radiomimetic Chemical (mechlorethamine)	
	Heat, Cold	
	Vascular Occlusion	
	Friction	
Mid Epidermis; Acantholysis	Pemphigus Vulgaris/Vegetans	loss of cellular cement (immune injury?)
	Benign Familial Pemphigus	
	Bowens Disease	cellular dysplasia
	Actinic Keratosis	
	Darier's Disease	genetically induced dyskeratosis
	Mild Thermal Damage	primary damage
Basement Zone; Injury to Basal Cells	Epidermolysis Bullosa Simplex	genetically induced
	Lichen Planus	inflammatory injury to basal cells (and basement zone)
	Lichen Sclerosis et Atrophicus	
	Lupus Erythematosus	
Basement Zone; Injury to Basement Membrane	Epidermolysis Bullosa Dystrophica (Dom)	genetically induced
	Urticaria Pigmentosa	mast cell degranulation
	Bullous Pemphigoid	unknown (immune ?
	Benign Mucosal Pemphigoid	injury to membrane)
	Suction	
Basement Zone; Injury to Upper Dermis	Erythema Multiforme	hypersensitivity-induced injury to dermis
	Adult Toxic Epidermal Necrolysis	
	Epidermolysis Bullosa Dys. (Res.)	genetically induced
	Dermatitis Herpetiformis	unknown (immune injury?)
	Porphyria Cutanea Tarda	phototoxic injury
	Moderate Thermal Damage	primary injury

C. Possible mechanisms of mid-epidermal separation.

1. Spongiosis

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2. Acantholysis

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II. Experimental Blister Formation

A. Mechanical

1. Friction blisters

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E. Neutral salts

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MAJOR BULLOUS DISEASES: Comparison of Clinical Features (modified from 66)

	Pemphigus Vulgaris/ Vegetans	Pemphigus Foliaceus/ Erythematosus	Bullous Pemphigoid	Dermatitis Herpetiformis	Erythema Multiforme
Distribution	Worldwide	Worldwide, endemic in Brazil	Worldwide	Worldwide	Worldwide
Ethnic	Common in Jews	---	---	---	---
Age	40-60	30-60 (Adolescents and young adults in Brazil)	60-80	20-50 men>women 2:1	All ages
Mode of Onset	Often localized at first may begin in mouth	Localized and slowly progressing usually scalp and face	Generalized, but often with prodrome of widespread erythema	Acute or gradual severe itching	Acute
Type of Eruption	Small flaccid bullae erosions persistant	Small flaccid bullae with scaling and crusting predominant	Large tense bullae remain intact but heal rapidly if ruptured	Small grouped vesicles erythema, urticarial papules leaves pigmentation	Erythema, wheals, bullae on erythematous base
Site of Eruption	Widespread	Scalp, face, upper trunk	Widespread	Extensor limbs, scapulae buttocks	Widespread, especially palms, soles, mouth
Mucous Membrane	Often primary	Uncommon	Uncommon	Rare	Common
Course	Deterioration and death untreated	Relatively benign spontaneous remissions possible	Recurrent attacks but relatively benign course	Remissions and exacerbations benign	Episodic attacks may last weeks may recur
Histologic Changes	Acantholysis with intraepidermal (suprabasalar) splitting	Acantholysis with subcorneal splitting	Subepidermal bulla with no acantholysis	Subepidermal bulla papillary microabsceses	Subepidermal bulla perivascular inflammation edema and necrosis of both epidermis and upper dermis

Major Bullous Diseases, cont'd.

	Pemphigus Vulgaris/ Vegetans	Pemphigus Foliaceus/ Erythematosus	Bullous Pemphigoid	Dermatitis Herpetiformis	Erythema Multiforme
Immunofluorescent Findings	Patient's serum contains IgG fixing in intercellular spaces of lower epidermis patient's lesions contain bound IgG but no complement- same location	Serum contains IgG fixing in intercellular spaces of upper epidermis Patient's lesions contain bound IgG same location	Patient's serum contains IgG fixing at basement zone Patient's lesions contain bound IgG same location Complement (C'3) also stainable in basement zone	Normal skin (not lesions) of patients contains bound globulin at and near basement zone	No immuno- fluorescent findings

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A. Pemphigus vulgaris

1. general classification

2. cutaneous findings

3. mucosal lesions

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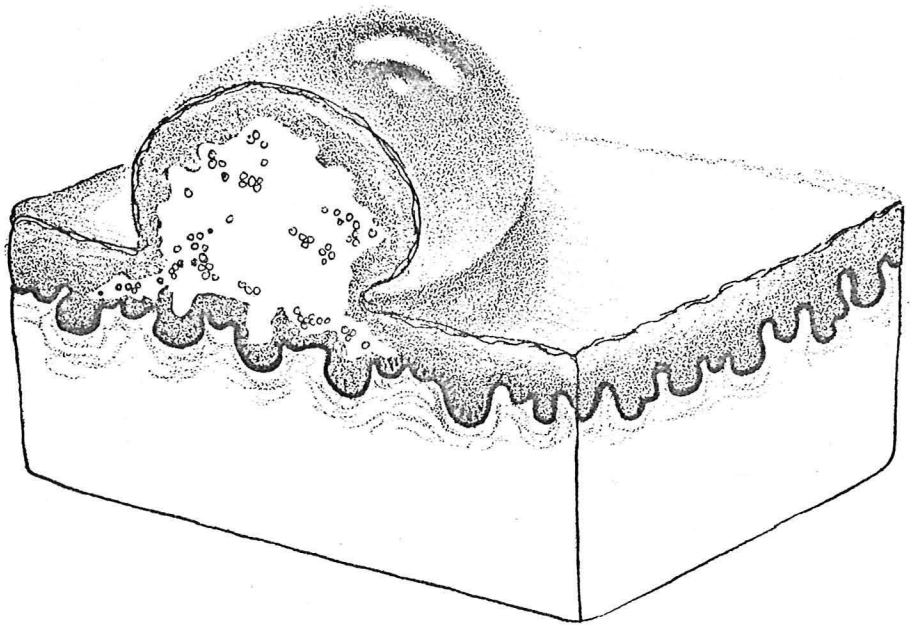
4. course



PEMPHIGUS VULGARIS

Clinical:

40 - 60 years
Jewish predominance
focal onset (mouth)
flaccid bullae, non-healing erosions
course inexorable

Pathology:

supra basalar acantholysis

Immunofluorescent findings:

serum and affected skin
γG intercellular antibody
complement not bound

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5. epidemiology

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6. differential diagnosis

B. Pemphigus Foliaceus

1. cutaneous lesions

2. mucosal lesions

3. course

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5. differential diagnosis

C. Pemphigus Erythematosus

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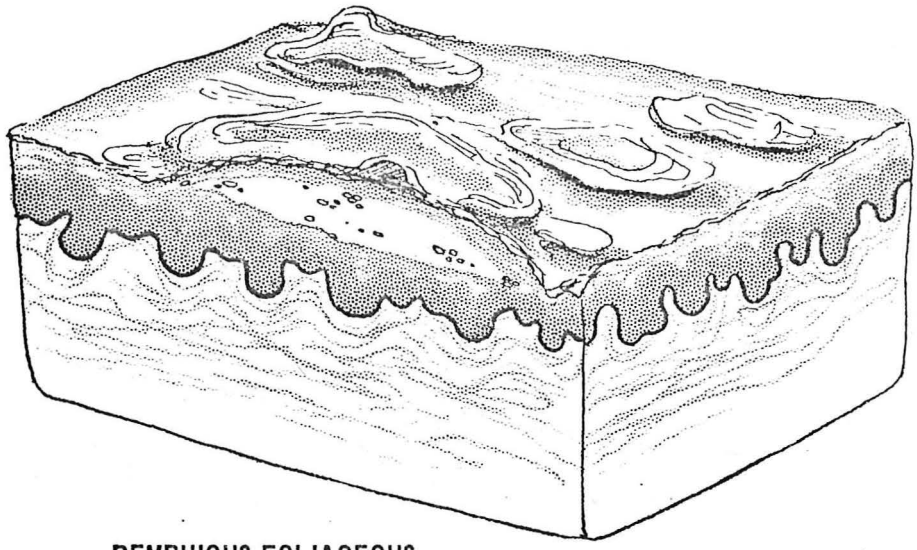

PEMPHIGUS FOLIACEOUS

Clinical:

30 - 60 years
endemic in Brazil (young persons)
focal onset (face)
few shallow bullae, more scaling, crusting
remissions occur

Pathology:

subcorneal acantrolysis

Immunofluorescent findings:

serum and affected skin
γG intercellular antibody (upper epidermis)
complement binding not established

D. Brazilian Pemphigus Foliaceus (Fogo Selvagem)

Reference

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E. Pathology of the Pemphigus Group.

Reference

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F. Immunofluorescent findings in Pemphigus

References

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G. Therapy

References

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H. Etiology

1. viral

References

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2. drug

3. association with LE, myasthenia gravis

Reference

91. Ziff, M. Medical grand rounds, May 27, 1971, and forthcoming editorial, Ann. Intern. Med.

IV. Pemphigoid

A. Bullous Pemphigoid

1. cutaneous lesions

2. oral lesions

Reference

92. Sklar, G., I. Meyer, and S. Zacarian. Oral lesions of bullous pemphigoid. Arch. Derm. 99:663-670, 1969.

B. Benign Mucosal Pemphigoid

Reference

93. Bean, S. F. Reported at Texas Dermatological Assoc. Meeting, 1971.

C. Pathology

Reference

94. Ritzenfeld, P. quoted in (65) p. 612

D. Immunofluorescent Findings

Reference

95. Jordan, R. E., C. T. Triftshauser, and Al Schroeter. Direct studies of pemphigus and bullous pemphigoid. Arch Derm. 103:486-492, 1971.

E. Therapy

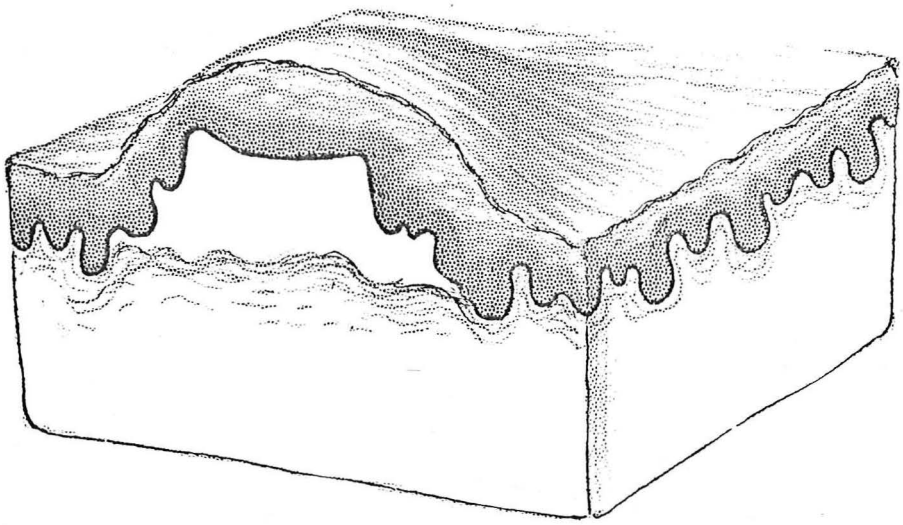
Reference

96. Greaves, M. W. Azathroprine in treatment of bullous pemphigoid. Brit. Med. J. 1:144-145, 1971.

F. Etiology

1. malignancy

2. LE



BULLOUS PEMPHIGOID

Clinical:

60 - 80 years
erythematous prodrome
generalized, tense bullae
erosions heal rapidly
remissions occur

Pathology:

subepidermal separation

Immunofluorescent findings:

serum and affected skin
IgG basement zone antibody
C'_3 found in lesion

Reference

97. Jordan, R. E., S. A. Muller, W. L. Hale et al. Bullous pemphigoid associated with systemic lupus erythematosus. Arch. Derm. 99:17-25, 1969.

3. pathogenic significance of the antibodies

V. Dermatitis Herpetiformis

A. Clinical Features

B. Epidemiology

C. Course

D. Differential Diagnosis

E. Pathology

Reference

98. Fry, L. and F. R. Johnson. Electronmicroscopic study of dermatitis herpetiformis. Brit. J. Derm. 81:44-50, 1969.

F. Immunofluorescent Findings

References

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101. Dick, H. M., N. G. Fraser, and D. Murray. Immunofluorescent antibody studies in dermatitis herpetiformis. Brit. J. Derm. 81:692-696, 1969.

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G. Association with Enteropathy

References

103. Johnson, D. P. and M. E. Alpert. Dermatitis herpetiformis-a disease associated with intestinal malabsorption. Am. J. Gastro. 55:21-32, 1971.

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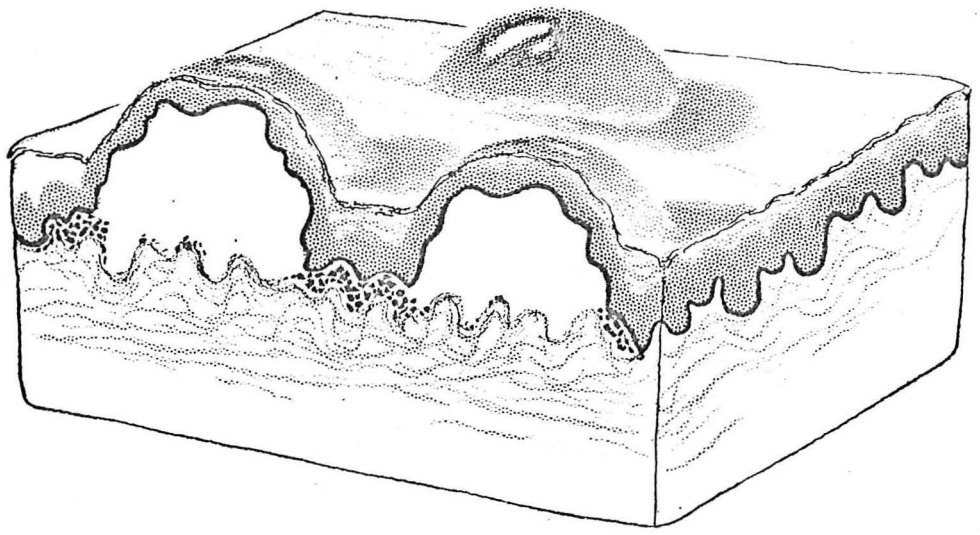

DERMATITIS HERPETIFORMIS

Clinical:

men 2:1 20 - 50 years
itching severe
grouped vesicles, papules, erythema
extensor surfaces
remissions and exacerbations

Pathology:

gastrointestinal involvement
subepidermal bullae
papillary microabscesses

Immunofluorescent findings:

normal skin (not serum or lesion)
γG antibody near basement zone

107. Marks, J., S. Shuster, and A. S. Watson. Small bowel changes in dermatitis herpetiformis. Lancet 2:1280-1282, 1966.

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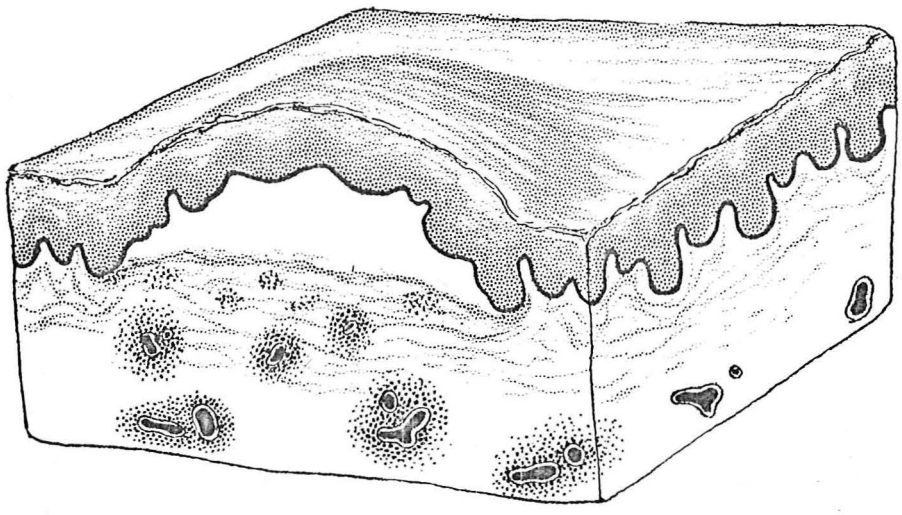

ERYTHEMA MULTIFORME

Clinical:

- all ages
- week onset
- erythema, wheals, bullae
- palms, soles, mouth

Pathology:

- subepidermal bullae
- dermal edema, necrosis, vascular damage

Immunofluorescent findings:

- none