FITZPATRICK'S

DERMATOLOGY IN GENERAL MEDICINE

FIFTH EDITION

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CHAPTER 59

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Stevens-Johnson Syndrome—Toxic Epidermal Necrolysis

DEFINITION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN; syn. Lyell's syndrome) are closely related severe, episodic acute mucocutaneous intolerance reactions most often elicited by drugs and less so by infections. Both are characterized by rapidly expanding macular rashes, often with atypical (flat, irregular) target lesions, and involvement of more than one mucosal site (oral, conjunctival, and anogenital). In TEN, the rash coalesces to widespread erythema, necrosis, and bullous detachment of the epidermis resembling scalding. Constitutional symptoms and internal organ involvement occur often and may be severe. SJS and TEN are in principle self-limited; the mortality rate is significant, however, and sequelae due to mucosal scarring may develop.

At present it is impossible to draw an absolutely sharp line of distinction between SJS-TEN and the more severe forms of erythema multiforme and thus to exclude SJS-TEN from the erythema multiforme spectrum. This issue is discussed in detail in Chap. 58.

CLASSIFICATION

TEN and SJS are tacitly or openly assumed by many authors to be identical and to differ only in severity.[1] Interestingly, nobody (except Lyell himself[2]) ever proposed to abandon the term *TEN* because it may be heterogeneous and include cases other than maximal variants of SJS—e.g., what has been called "TEN without spots."[3] Circumspection has thus been recommended.[4] On the other hand, most cases of TEN are likely to develop from SJS[3]; therefore, and because clear distinction of these entities is impossible in most of the reported series, both are dealt with together in this chapter.

Supposing that qualitatively SJS and TEN are identical disorders, a definition of these entities on quantitative grounds was proposed:[3,5] *SJS* is reserved for cases of <10% body-surface involvement and *TEN* for those of >30%; those with an extent of 10 to 30% were labeled "SJS-TEN overlap." Although somewhat artificial, this classification is useful for epidemiologic purposes because the fraction of body surface involved is a major prognostic factor in SJS-TEN. Also, it corresponds to a classification earlier proposed by one of us (R.R.M.).[6]

INCIDENCE AND EPIDEMIOLOGY

Few investigations are available on the epidemiology of SJS-TEN, and not all of them use the same classification system.[7–14] The average incidence of SJS may be estimated at 1 to 2 per million of the population per year and that of TEN at 0.5 to 1.4 per million per year. In Germany, the cumulative incidence of SJS-TEN was found to be 1.9 per million per year; the proportional relative incidences of SJS, SJS-TEN overlap, and TEN were 3:2:17. There is no ethnic preponderance; females appear to be about twice as frequently affected as males.[12,15] SJS-TEN is most often found in adults, but its occurrence in children is not infrequent.[6] SJS-TEN typically occurs sporadically, but epidemics have been observed with the mass use of drugs.[16,17] SJS-TEN is a single event in most cases; in case of reexposure to the culprit drug, SJS-TEN takes a more severe course.[18] The incidence is dramatically increased in the HIV-infected population[19–22]; it has been estimated at three orders of magnitude higher in Germany.[23] SJS-TEN was found to be associated with the HLA-A29 and -B12 (relative risk, 13.4) and the HLA-B12 and DR7 haplotypes.[24]

Population-based and case-control studies on SJS-TEN have been initiated in the United States and Europe. These are likely to clarify pending issues of epidemiology and drug etiology.[25,26]

ETIOLOGY

SJS-TEN is a polyetiologic reaction pattern. Drugs are clearly the leading causative factor (80 to 95 percent of patients with TEN, >50 percent with SJS) (Table 59-1), and only a minority of cases appear to be linked to infection, vaccination, or graft-versus-host disease (GVHD). In a small fraction of SJS-TEN (<5% for TEN), neither drugs nor other potential causes become apparent (idiopathic SJS-TEN). The identification of the responsible trigger factors is hampered by the lack of appropriate diagnostic in vitro and skin tests. Circumstantial evidence or simple temporal coincidence therefore usually serves as the only criterion. Thus, despite the wide range of factors implicated, the evidence appears compelling in only a few instances.

Whereas the causative role of drugs is undebated, considerable uncertainty exists about quantitative aspects, for instance, the risk associated with individual drugs to provoke SJS-TEN and the role of accompanying factors that may influence this risk. Obviously, the many case reports, in which over 100 drugs have been found to elicit SJS-TEN, do not provide this information. Population-based studies may serve this purpose if the incidence of SJS-TEN is calculated per drug user or per daily drug dose consumed in the population. Such calculations may give rough estimates; their predictive value is limited, though, if the incidence of adverse events in question is very low.[25] In this dilemma, case-control studies have been considered to be the most powerful tool[25,26]: relative risks are calculated from the drugs taken by index patients and compared with those taken by control patients selected from the same hospital environment; multivariate analysis is designed to help take into account associated factors such as intake of several drugs, age, and accompanying illnesses. Several such case-control studies have been initiated and one has been published.[28] More data are definitely needed before any conclusions can be drawn.

TABLE 59-1

Drugs Associated with Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

DRUGS MOST FREQUENTLY ASSOCIATED*	DRUGS ALSO ASSOCIATED
Sulfadoxine	Cephalosporins
Sulfadiazine	Fluoroquinolones
Sulfasalazine	Vancomycin
Co-trimoxazole	Rifampin
Hydantoins	Ethambutol
Carbamazepine	Fenbufen
Barbiturates	Tenoxicam
Benoxaprofen†	Tiaprofenic acid
Phenylbutazone	Diclofenac
Isoxicam†	Sulindac
Piroxicam	Ibuprofen
Chlormezanone	Ketoprofen
Allopurinol	Naproxen
Amithiozone	Thiabendazole
Aminopenicillins	

*Together these drugs account for approximately two-thirds of the cases attributed to drugs in large series in France, Germany, and the United States.
†This drug is no longer marketed.
SOURCE: Roujeau et al.[27]

Obviously, the list of culprit drugs is subject to change with region and time, but three major groups and a few odd drugs appear to be of universal relevance. Sulfa drugs, particularly long-acting sulfonamides and co-trimoxazole, are cited as the most common triggers in all surveys and reviews. The incidence of SJS-TEN has been estimated at between 1 and 10 per 100,000 users[28]; the relative risk is 172.[28] Particularly aggressive and often fatal cases have been observed in HIV-infected patients, in the context of the treatment of *Pneumocystis carinii* infection,[19] and in malaria prophylaxis.[29]

Anticonvulsive drugs such as phenytoin, carbamazepine, and phenobarbital seem to carry equally high risks; their relative risks were calculated to be from 11 to 15.[28] In contrast to this, carbamazepine was found to elicit the highest incidence of SJS-TEN per user (14 per 100,000).[27] Hydantoins are considered the main cause of TEN in children.[6] Severe SJS-TEN has been described in a series of patients who received phenytoin simultaneously with cranial irradiation.[30] Valproic acid, often used as an alternative for hydantoins, was found to have an equally high relative risk.[27]

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as butazone and oxicam derivatives were often found to be inciting drugs; isoxicam, for instance, was withdrawn in France following 13 cases of TEN[10,31]; their relevance was confirmed in the case-control study (relative risk for oxicam derivatives, 18) but less so for propionic acid derivatives (relative risk, 4.5). Pyrazolones and salicylates, formerly often thought to cause SJS-TEN, had only low relative risks (2).[28] Chlormezanone (a tranquilizer unrelated to benzodiazepines)

and allopurinol are important causes of SJS-TEN in developed countries,[28,32] whereas antituberculosis drugs play an important role in Third World countries.[33] Antibiotics have been more often suspected than actually causative; relevant risks may exist for ampicillin, macrolides, and quinolones.[27] In 3 of 20 cases of TEN observed in Singapore, Chinese herbs were found to be responsible.[8] A variety of other agents, such as endocrine agents, chinine-containing beverages,[34] airborne toxins,[35] and contact allergens and toxins, have been implicated in the etiology of SJS-TEN.

It is a likely drawback of the statistical approach to the etiology of SJS-TEN that drugs that may have been taken during the prodromal phase to alleviate symptoms cannot be distinguished from those that actually caused the disease. The often-listed antibiotics, pyrazolones, and salicylates may be such cases. We suspect that the same holds true for systemic glucocorticoids, which were found to be associated with a surprisingly high relative risk of 12.[28]

Infectious agents play a much less prominent role as inciting factors in SJS-TEN. The most thoroughly documented cases have been those precipitated by *Mycoplasma pneumoniae*,[36] which has also been isolated from the lesions of SJS-TEN.[37] Less well documented cases have been linked to histoplasmosis,[38] adenovirus infections, hepatitis A,[39] infectious mononucleosis,[40] coxsackievirus B5,[41] gram-negative septicemia,[42] milker's nodules,[43] and yersiniosis.[44] The link to other infectious agents is more tenuous.

The issue of individual predisposing factors that may promote the development of SJS-TEN has not been thoroughly addressed. Although familial occurrence is rarely a feature of SJS-TEN,[45,46] there is the possibility of a genetic susceptibility, as documented by the association with certain HLA haplotypes.[28] Synergistic effects (e.g., viral infection and drug intake[47]) and drug interactions are likely to play roles in many cases (in one study patients took a mean of 4.4 drugs prior to the onset of TEN[31]). Physical factors such as exposure to ultraviolet light[48] and x-rays[30,49–51] may precipitate drug-induced SJS-TEN, with the skin lesions being of maximal intensity at the sites of exposure. Also, SJS-TEN appears to occur preferentially in patients with multiple conditions; accompanying diseases are often those with immune activation, such as collagen vascular diseases, neoplasia and lymphoma, acute GVHD, and even vaccination.[52,53]

Acute GVHD is an obviously rare but interesting cause of SJS-TEN[54]; according to one survey,[55] TEN occurred in 9 of 152 allogeneic bone marrow recipients and may thus be more frequent than previously suspected. The relationship between acute GVHD and TEN is conceptually difficult to assess because skin lesions are nearly indistinguishable both clinically and histologically; the differences between the two entities pertain more to type and severity of internal organ involvement (gastrointestinal tract, liver) than to skin involvement. Since all bone marrow allograft recipients are subject to factors that in their own right (or synergistically) may precipitate TEN (x-rays, cytotoxic drugs, often also infections like cytomegalovirus), it is impossible to decide which role is to be ascribed to GVHD. It is clear, however, that TEN may result from acute GVHD independently from drug intake: it was observed in a patient with thymus hypoplasia who took no drugs[56] and can be reproduced in an animal model for acute GVHD.[57] TEN in acute GVHD has been shown to have a 100% mortality rate.

Identification of the provocative agent rests mainly on history since skin testing and in vitro tests are usually not helpful,[58,59] and exposure tests are ethically unacceptable. Exceptional reports describe positive intracutaneous and patch tests[60,61] and positive lymphocyte transformation tests[61] or increased lymphocyte susceptibility to cytotoxic killing by liver microsome-induced drug intermediates[60] in patients with drug-induced TEN.

PATHOGENESIS

The pathomechanisms operative in SJS-TEN are only partially resolved. There are analogies to the mechanisms of herpes simplex virus (HSV)–related erythema multiforme (EM), but important differences have become apparent. Like EM, SJS-TEN is viewed as a cytotoxic immune reaction aimed at the destruction of keratinocytes expressing foreign (drug-related) antigens, with little evidence for a role of humoral immunity. An immune genesis is also suggested by the characteristic lag between exposure and disease onset (1 to 45 days; mean, 14), which tends to be much briefer in the rare instances of repeated exposure. Drug-specific T cell activation (interestingly including both CD4+ and CD8+) has been shown in vitro on peripheral blood mononuclear cells of patients with bullous drug eruptions[62]; a high rate of production of interleukin-5 in addition to other cytokines was noted. As in HSV-related EM, epidermal injury is based on the induction of apoptosis[63,64]; furthermore, in both conditions, dermal mononuclear cells were found to be dominated by memory CD4+ lymphocytes, whereas CD8+ cytotoxic cells (and large granular lymphocytes[65]) were prevalent in the epidermis.[66,67] In both conditions epidermal keratinocytes express ICAM-1 and MHC class II antigens; Langerhans cells are notably reduced or absent.[67]

It has always puzzled investigators how the relatively few cytotoxic cells present in the epidermis of patients with SJS-TEN may induce an epidermal injury far in excess of that of EM, which features many more such effector cells. Paquet et al.[68,69] demonstrated that in SJS-TEN, in contrast to EM, inflammatory cells contain large numbers of activated macrophages and factor XIII+ dendrocytes; there is a drastic overexpression of tumor necrosis factor α (TNFα) in the epidermis, while only minute amounts of this cytokine are found in EM. TNFα is thus likely to play an important role in epidermal destruction, by inducing apoptosis directly or by attracting cytotoxic effector cells, or both. The source of TNFα may be both macrophages and keratinocytes; mutual stimulation is likely. In this context, it is interesting that physical factors that precipitate or drastically accentuate drug-induced SJS-TEN are known to stimulate TNFα expression in keratinocytes (ultraviolet light and x-rays).

The nature of the antigens that drive the cytotoxic cellular immune reaction is not well understood. It has been proposed that drugs or their metabolites act as haptens and render keratinocytes antigenic by binding to their surface.[53,70] Obviously, the drug-modified peptide may be presented on both major histocompatibility complex (MHC) I and MHC II molecules.[62] Shear et al.[53] linked cutaneous drug eruptions to a defect of the detoxification systems (in both liver and skin): aromatic drug metabolism by cytochrome P_{450} leads to formation of reactive hydroxylamines from sulfonamides or arene oxides from aromatic anticonvulsants that bind to cell constituents if not rapidly detoxified by epoxide hydrolases. Genetically determined defective detoxification may thus result in direct toxicity or alteration of the antigenic properties of keratinocytes. This attractive hypothesis remains to be proven; it is supported by the association of SJS-TEN with the carbamazepine or hydantoin hypersensitivity syndromes,[71–74] the association with the slow acetylator phenotype in sulfonamide-triggered SJS-TEN,[75] preliminary results of in vitro cytotoxicity assays,[76] and the overproportional occurrence in HIV-infected patients who are deficient

in glutathione, an important scavenger of toxic compounds.[77,78] It has been hypothesized that the cytotoxic assault may be directed at viral antigens that persist in skin structures.[47] Although drug-induced SJS-TEN occasionally occurs in animals,[79] no animal model is available at present.

Autoantibodies against desmoplakin I and II have been detected in a subset of SJS.[80,81] In these cases, suprabasal acantholysis was present, while the clinical disease was no different from other patients with SJS who lack these antibodies. While pathogenic relevance of these autoantibodies seems to be established for this subset of SJS[82] it is not clear as yet how these patients differ from other patients with SJS.

CLINICAL FEATURES (See Table 59-1)

SJS-TEN begins with a nonspecific prodrome of 1 to 14 days in at least half of the patients: fever, malaise, headache, rhinitis, cough, sore throat, chest pain, vomiting, diarrhea, myalgias, and arthralgias. Patients often feel ill and receive antimicrobial and anti-inflammatory treatment that, later, may cause difficulties in determining the offending factor. The onset of disease is sudden; its severity varies within wide limits in terms of brevity of the lag period between exposure and onset of the eruption, rapidity of evolvement, total body-surface area involved and degree of confluence, prominence of mucous membrane involvement, accompanying constitutional symptoms, and internal organ involvement.

A macular, at times morbilliform rash appears first on the face, neck, chin, and central trunk areas and may then spread to the extremities and the rest of the body. The individual lesions are reminiscent of target lesions due to their dusky centers or are mere roundish, irregularly shaped and moderately well defined pale livid macules (Fig. 59-1).[3,5] They are often larger than target lesions, flat, and tender and exhibit a positive Nikolski sign (Fig. 59-1*B*; 59-2*B*); some form flaccid and occasionally hemorrhagic blisters. Despite these obvious differences from EM, occasional raised atypical targets or even typical target lesions may be found.[5] The lesions rapidly increase in numbers and size; maximal disease expression is usually reached within 4 to 5 days, but new crops may emerge considerably later if a long-acting drug is the inciting agent. There is a striking tendency for coalescence; confluence is only partial and limited to the predilection sites (face, neck, chest) in SJS, but widespread to total in TEN (Fig. 59-2). Areas of confluence represent extensive diffuse erythemas; individual macular lesions still remain discernible in the periphery. Within such lesions, the epidermis becomes loose and easily detached following minimal frictional trauma. Large flaccid blisters form; the blister roofs turn necrotic and rupture easily. Sheets of necrotic epidermis slide off the face and at pressure points such as the back and shoulders, leaving intensely red, oozing erosions (Fig. 59-2*C*). Denudations may involve 10 to 90 percent of the body surface. In severe cases of TEN, prominent involvement of the skin appendages is seen: shedding of finger- and toenails and loss of eyebrows and cilia (Fig. 59-2*B*).

The rash is paralleled or even preceded by mucous membrane lesions. The oral cavity (buccal mucosa, palate) and the vermilion border of the lips (Figs. 59-1*C*; 59-2*B*) are almost invariably affected, while less often the bulbar conjunctiva and anogenital mucosae are involved. All three sites are involved in approximately 40 percent of cases.[83] Heralding signs are sore and burning sensations of the conjunctivae, lips, and buccal mucosa; edema; and erythema, followed by blisters that rupture and transform into extensive, hemorrhagic dull red erosions coated by grayish-white pseudomembranes (necrotic epithelium and fibrin) (Fig. 59-1*C*) or shallow aphthous-like ulcers. The lips are covered by characteristic massive hemorrhagic crusts. Oral lesions are severely painful and cause eating and breathing difficulties and hypersalivation. If more severe, the process may extend to the gingiva, tongue, pharynx, nasal cavity, and even to the larynx, esophagus, and respiratory tree. Otitis media may be seen. Conjunctival involvement features inflammation and chemosis, vesiculation and painful erosions, and bilateral lacrimation. Less common are purulent conjunctivitis with photophobia and/or psuedomembranes, corneal ulceration, anterior uveitis, and panophthalmitis. Genital involvement most often includes painful hemorrhagic bullous-erosive or purulent lesions of the fossa navicularis and glans penis in males, or the vulva and vagina in females and may lead to urinary retention and phimosis. Anal erosions are less frequent.

Extracutaneous Symptoms

Constitutional signs include fever, arthralgias, weakness, and prostration. Internal organ involvement is rare in SJS but may be severe in TEN, most often affecting the respiratory and gastrointestinal tracts. Tracheal and bronchial symptoms include breathing difficulties, sloughing of the respiratory tract mucosa leading to persistent cough, bronchial obstruction and expectoration of bronchial casts,[84] adult respiratory distress syndrome,[85] tracheitis, patchy pulmonary disease, bronchopneumonia, and pneumothorax. Less commonly, ileal involvement, diarrhea, abdominal pain, esophageal and gastrointestinal bleeding, colonic perforation, melena, and hepatitis have been reported.[86,87] Toxicity, dehydration, and water and electrolyte imbalance may proceed to hemodynamic shock, pulmonary edema, mental obtusion, confusion, coma, and seizures. Myocarditis and myocardial infarction are frequently seen in fatal cases, although they are generally uncommon. Except for microalbuminuria, renal complications are rare[88]; if present they are more often linked to septicemia or septic shock rather than to TEN. Acute tubular necrosis, membranous glomerulonephritis, and renal failure have been described.[89]

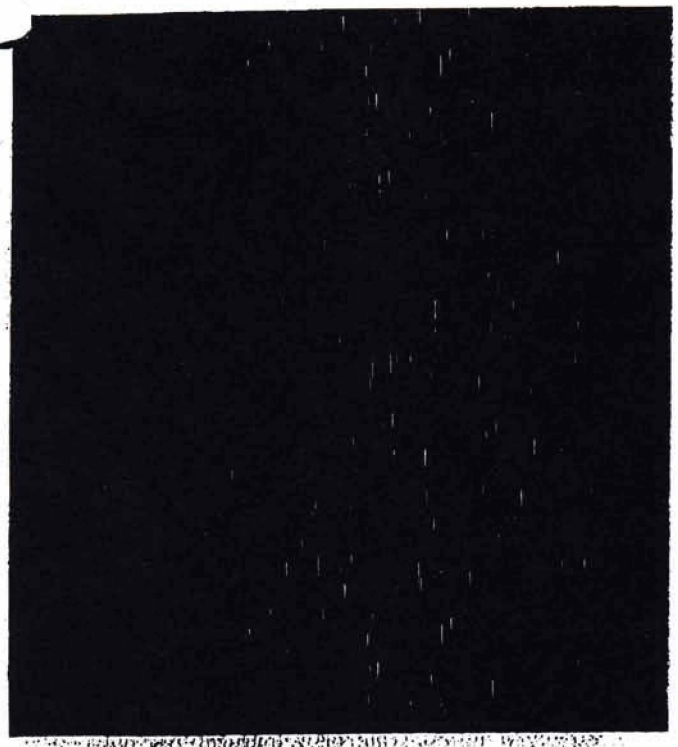
Late Complications

Skin lesions heal with transitory hyper- and/or hypopigmentation. Scarring does not usually appear except in extensive cases with secondary infection, where contractures, alopecia, and anonychia may develop. Scarring is a characteristic and frequent (in up to 30% of cases of TEN) late complication of mucosal lesions, which is most serious in the eyes: symblepharon, synechiae, entropion and ectropion, trichiasis, corneal opacities or scarring, and pannus formation potentially result in blindness. Lesions of the lips and oral mucosa usually resolve without sequelae, but esophageal, bronchial, vaginal, urethral, and anal strictures develop at times. A Sjögren-like syndrome may develop as the result of damage to the salivary and lacrimal glands.

TEN Without Spots

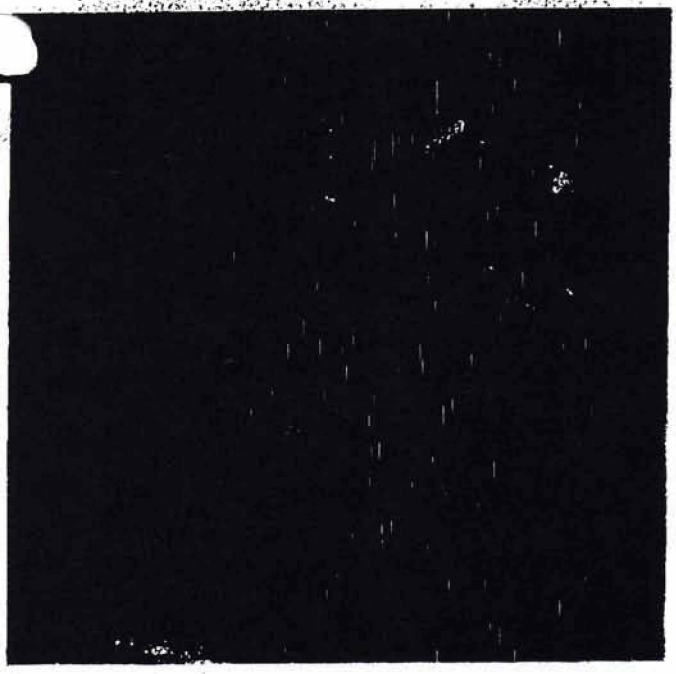
In a small minority of cases, TEN does not arise from confluent lesions of SJS but presents with primary ill-demarcated diffuse erythemas that are rapidly progressive and may become erythrodermic. Mucous membranes may sometimes remain unaffected. A trickle of such cases have been recorded through the decades, but it is still an ill-defined entity. It may affect predominantly elderly

FIGURE 59-1



A.

B.



C.

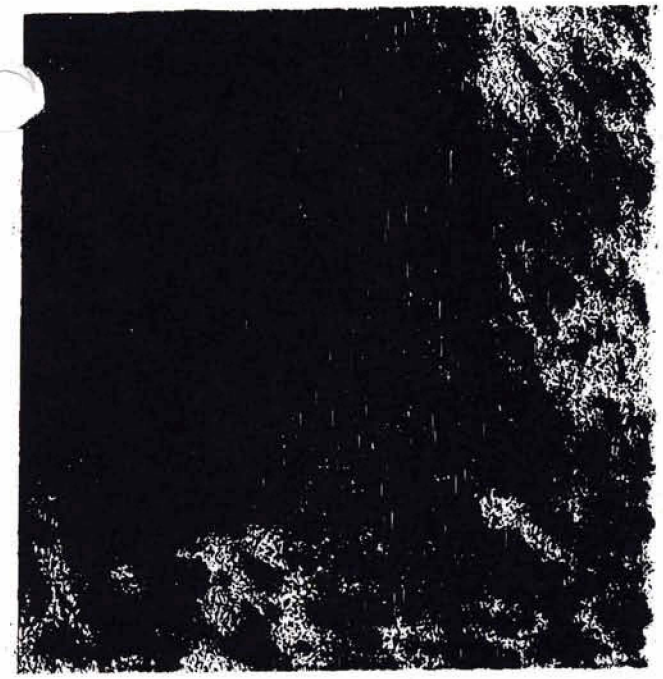
Stevens-Johnson syndrome. *A.* Initial stage: partially confluent erythematous lesions with dusky centers, presenting as flat atypical target lesions. A positive Nikolsky sign can be recognized. *B.* Advanced stage: generalized macular eruption with detachment of necrotic epidermis. *C.* Extensive necrosis and erosions of the lips and oral mucosa.

males; and may be triggered by the same drugs as SJS-TEN, but opathic" cases may occur more often. The majority of cases of N caused by the graft-versus-host reaction may represent this type of TEN.[55] The prognosis may be worse than that of SJS-TEN. The differential diagnosis to generalized fixed drug eruption is equivocal; it rests mainly on the presence of prominent systemic signs.

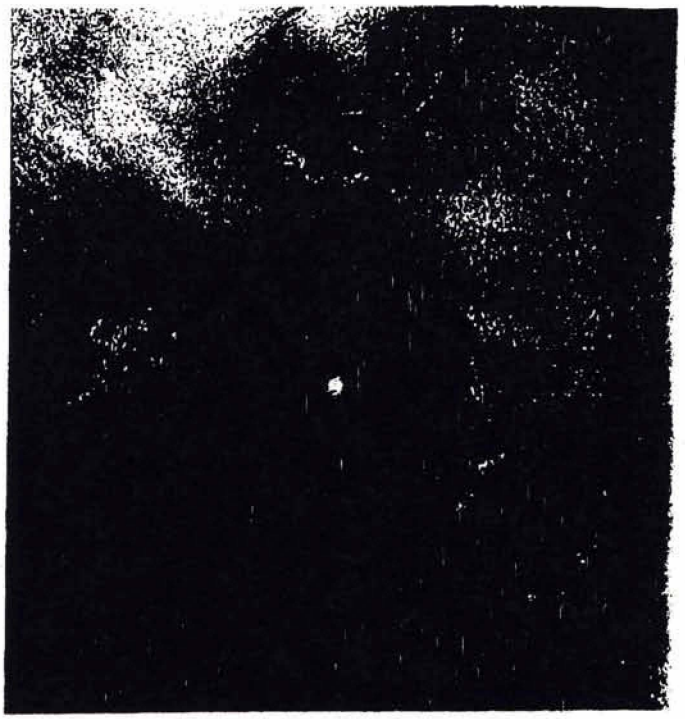
PATHOLOGY

Histopathology of SJS-TEN is characterized by prominent epidermal necrosis, which contrasts to only scanty signs of inflammation in both epidermis and dermis. Epidermal injury may present as sat-

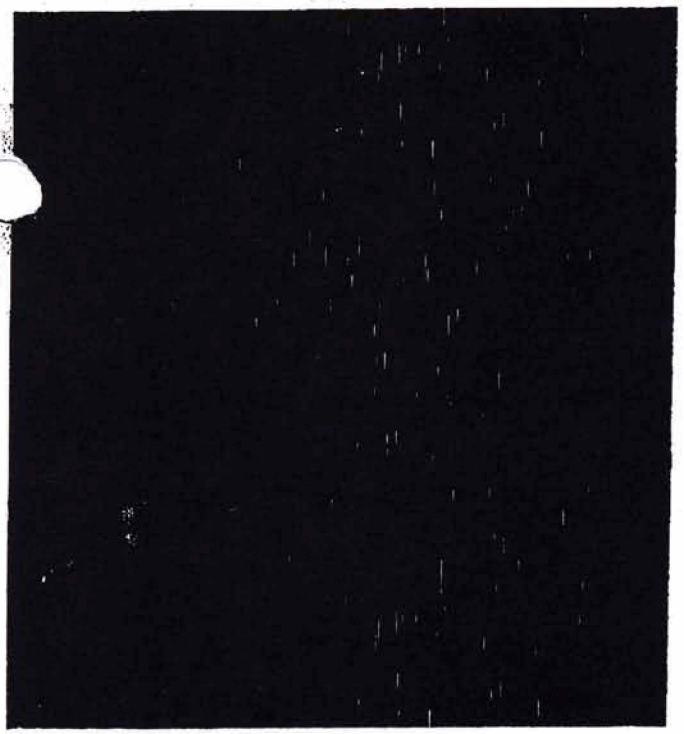
FIGURE 59-2



A.



B.



C.

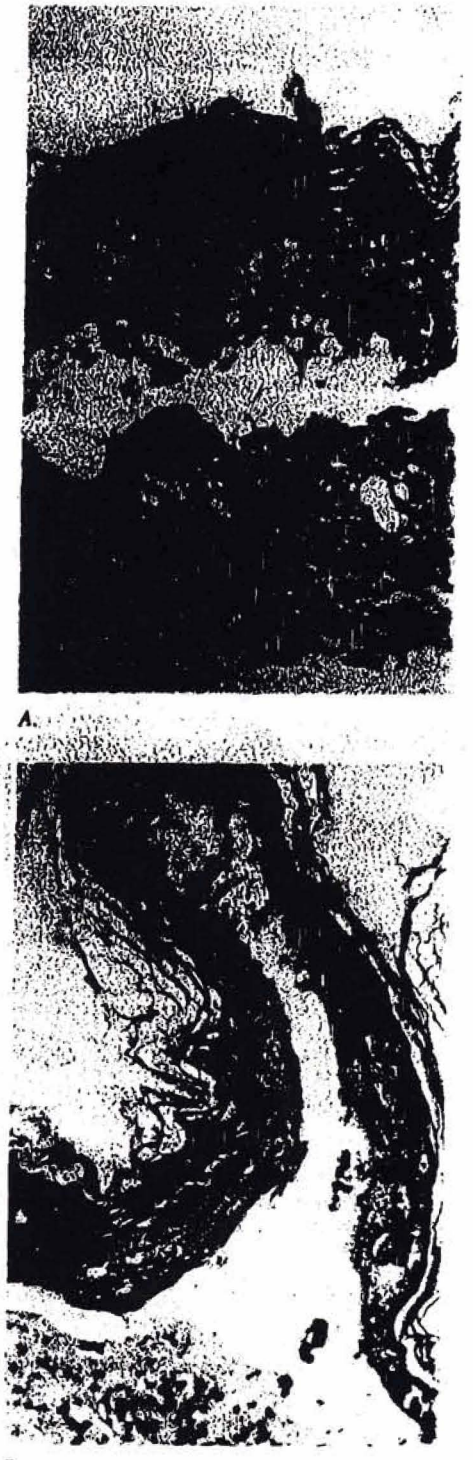
Toxic epidermal necrolysis. *A.* Confluent morbilliform eruption; note positive Nikolsky sign. *B.* Diffuse erythema of face with shedding of cilia and epidermis of eyelids, severe erosions, and hemorrhagic crusting of the lips. *C.* Diffuse generalized shedding of the epidermis reminiscent of scalding.

ellite-cell necrosis in early stages and progresses to more extensive eosinophilic necrosis of the basal and suprabasal layers; subepidermal separation may be observed (Fig. 59-3). In TEN, there is total thickness necrosis and sloughing of the epidermis. There is a mod-ely dense to sparse mononuclear cell infiltrate in the papillary lis, with exocytosis into the epidermis. Spongiosis and dermal edema are most often absent. Neutrophils and nuclear dust are occasionally seen.

Extracutaneous Pathology

In severe SJS-TEN, extensive fibrinoid necrosis may occur in several internal organs, including stomach, spleen, trachea, and bronchi.[90] Acute tubular necrosis was found in one patient with renal failure. Despite the frequency of pulmonary radiologic abnormalities, the pathology in uncomplicated cases is limited to sparse mononuclear cell infiltrates.

FIGURE 59-3



A.

B.

logic appearance of TEN in the peak stage: eosinophilic necrosis epidermis with little inflammatory response in the dermis. Note vage in the junction zone. *B*. The completely necrotic epidermis has detached from the dermis and folded like a sheet.

LABORATORY INVESTIGATIONS

SJS-TEN is invariably accompanied by an elevated blood sedimentation rate and may show moderate leukocytosis, fluid-electrolyte imbalances, microalbuminuria, hypoproteinemia, elevation of liver transaminases, and anemia. In the acute phase, patients with TEN may have a transient decrease of peripheral CD4+ T lymphocyte counts, accompanied by reduced allogeneic and natural-killer-cell cytotoxicity, which return to normal after 7 to 10 days.[91] These laboratory abnormalities resemble, to some degree, those found in second-degree burn injuries[92]; it must be noted, though, that they are usually less severe (and thus do not automatically warrant intensive care in a specialized burn center). Neutropenia occurs in a minority of cases and is then regarded as an unfavorable prognostic sign.[83] Eosinophilia may be found in some cases, and circulating immune complexes have been demonstrated in several reports but are not, in general, accompanied by complement consumption. Renal abnormalities such as proteinuria and elevated blood urea nitrogen levels occur in about 5 percent of cases.[83] A host of other laboratory findings may be abnormal as involvement of internal organs or secondary infection become manifest.

DIFFERENTIAL DIAGNOSIS

Diagnosis of SJS-TEN (including the distinction from EM; Tables 58-1 and 59-2), is usually straightforward. Prior to confluence and vesiculation, SJS-TEN may be confused with other morbilliform drug eruptions; a positive Nikolski sign and skin tenderness of early macular lesions are important clues. Once the peak stage is reached, only few entities need to be reasonably considered in the differential diagnosis, as described below.

Generalized Bullous Fixed Drug Eruption

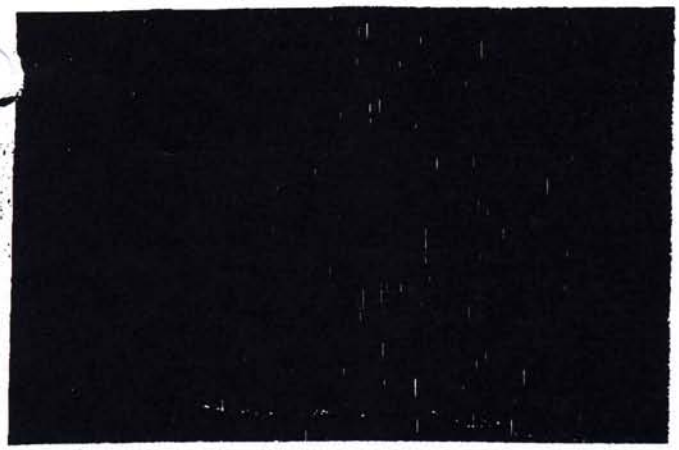
This most extensive form of fixed drug eruption can be mistaken for TEN if widely confluent; many studies of SJS-TEN may contain such patients, particularly those with recurrences.[93] It is characterized by multiple large, ill-defined, dull purplish-livid patches, at times with flaccid blisters (Fig. 59-4). The distribution is often symmetric, with a predilection for the acral extremities, genitals, and intertriginous sites. Mucosal sites are usually spared and constitutional symptoms are mild. Recovery is rapid and complete, without sequelae. The medical history reveals drug intake (most often sulfonamides, barbiturates, quinine, and butazones) and prior episodes at the same sites but of lesser extent following the intake of the culprit drug. Differential diagnosis is made on clinical and histo-

TABLE 59-2

Differential Diagnosis SJS-TEN

SJS	TEN
Erythema multiforme	Staphylococcal scalded-skin syndrome
Viral exanthems	Generalized fixed drug eruption
Ampicillin rash	Burns, cauterization, etc.
Macular drug eruptions	Toxic erythroderma
Fixed drug eruption	
Acute GVHD	

FIGURE 59-4



Generalized bullous fixed drug eruption. Note ill-defined large erythemas with epidermal detachment.

logic grounds; histopathology reveals features resembling SJS-TEN and, in addition, prominent edema of the papillary dermis.

Staphylococcal Scalded-Skin Syndrome

This is an unrelated disorder caused by staphylococcal epidermolysin toxinemia and characterized by subcorneal acantholysis. It occurs almost exclusively in children and may be confused with SJS-TEN because of a resemblance to scalding that is common to both. Differential diagnosis is facilitated by a wide range of clinical criteria. In ambiguous cases, it can be rapidly achieved by exfoliative cytology or frozen sections of biopsy material (see Chap. 96).

Scalding, Kerosene or Paraffin Burns,[94] and Exposure to Caustic Agents[35]

Differential diagnosis rests on the artificial distribution, the absence of a preceding rash, and the lack of skin appendage involvement in these conditions.

TREATMENT

Obviously, identification of the provocative agent must be attempted. Suspected drugs must be withdrawn, and infections appropriately treated if treatment is available. Care of patients with SJS-TEN is difficult and complex and requires considerable experience and flexibility to adjust for individual problems. Controlled prospective treatment studies are absent, as are generally accepted guidelines.[95]

Whereas very mild cases of SJS-TEN may be treated on an outpatient basis, admission to dermatology units in hospitals is mandatory for the majority of cases, if available (which is the case in most European countries); intensive care in burn units, as recommended particularly by plastic surgeons,[96] may be advisable in special situations but not generally so. Although it has often been claimed, it cannot be concluded from the literature that mortality rates are higher in dermatologic wards than in intensive care units.

The rationale for treating patients with TEN in burn units would be to apply the therapeutic principles of burn injuries—i.e., rigorous adjustment of fluid, protein, and electrolyte balance; fending off infection; and early surgical debridement of skin lesions. This rationale is at best questionable, however, because second-degree burns and TEN are pathophysiologically different despite their clinical similarity: in burns, prominent vascular damage is responsible for drastic fluid, electrolyte, and protein imbalances; in TEN, however, vascular damage is much milder, resulting, in our experience and that of others,[97] in much less edema and less-drastic laboratory anomalies than burns of equal extent. Moreover, necrosis does not extend to the dermis; as a rule, spontaneous reepithelialization is rapid and surgical intervention is thus not necessary to expedite healing. Finally, burns result from a single thermal trauma, whereas TEN represents an immunologic attack that may progress for more than a week (not just 3 to 4 days, as often claimed[28]), depending on detoxification and excretion of the offending agent. It should be the treatment strategy in this early phase to halt disease progression and thus limit the extent of skin and mucosal necrosis and reduce the severity of sequelae. It is the clinical experience of numerous authors including one of us (P.O.F.) that glucocorticoids may in fact curb disease progression, albeit often only in relatively high doses (e.g., 100 mg of methylprednisolone per day). Obviously, glucocorticoids may promote the risk of infection (pneumonia, septicemia); they should thus be tapered immediately after disease progression is halted, and prophylactic antibiotics should be given. Pursuing this strategy, the mortality rate of TEN was kept at <10 percent in our institution throughout the past two decades. The use of systemic glucocorticoids, however, has became controversial; they are no longer recommended by many authors,[6,15,28,83,97–103] whereas others continue to do so.[104–111] It is often argued that patients treated with systemic glucocorticoids fare worse than those without; the use of glucocorticoids has been called "detrimental,"[70] whereas for others it is "lifesaving."[104] Also, SJS-TEN has been observed in patients already being treated with glucocorticoids for another underlying disease.[112,113] It must be said that mortality rates are highly different in published series of patients, ranging from zero to more than 50 percent, as are the therapeutic regimens used; it is impossible at present to correlate any particular therapeutic measure with the outcomes reported. According to our view, agreement should be reached on the following treatment principles in SJS-TEN:

1. Treatment in burn units should be strived for in exceptional cases but is not generally necessary.
2. Treatment has to be individually tailored according to cause, type and stage, and presence and type of complications.
3. Systemic glucocorticoids should not be used routinely but are justified in the early stages of drug-induced SJS-TEN. They should be given in doses from 80 to 120 mg of methylprednisolone per day by mouth for several days until disease progression has ceased. Doses ought to be tapered quickly but cautiously since no further benefit can be expected thereafter, and the untoward effects may then predominate.
4. Treatment must focus on early detection and prevention of the most common fatal complications, e.g., overwhelming infection. Thus, prophylactic antibiotic treatment should be started right from the beginning, before signs of infection manifest. Sulfonamides and antibiotics with known sensitizing potential must be avoided (aminopenicillin, cephalosporins, macrolides, quinolones). Cultures from skin and mucosal erosions, blood,

and sputum must be regularly performed and the antibiotic treatment adjusted accordingly.

5. Hematocrit, blood gases and fluid, electrolytes, and protein balance must be monitored and adjusted appropriately. Fluid-replacement regimens as used for burn patients should not be used. Central venous lines and urinary catheters should not be routinely inserted.
6. Supportive care is of great importance; particular attention must be directed to pulmonary care (suctioning, postural drainage, etc.), ophthalmologic preventive measures (ocular lubricants, sweeping of conjunctival fornices, and removal of fresh adhesions, etc.), and high-calorie and high-protein diet.
7. Debridement of necrotic skin should not be performed before disease activity ceases.

Topical treatment may be carried out with hydrocolloid or, more conservatively, with gauze dressings. Obviously, sulfonamide-containing topical agents should be avoided. Patients should be placed on aluminum sheets. Cadaver allograft skin[114] and porcine allografts[99] have been advocated, but their use is of questionable benefit.[97] Alternative systemic treatment methods for the acute phase of SJS-TEN are still experimental and include hemodialysis, plasmapheresis,[115] cyclophosphamide,[116] and cyclosporine.[117,118] The use of *N*-acetylcysteine has been proposed to increase the intracellular glutathione levels and thus to augment the antioxidant and detoxifying capacities of this amino acid; another effect of glutathione is the inhibition of TNFα production.[119] Granulocyte colony-stimulating factor has been recommended for the treatment of severe SJS-TEN with neutropenia.[120]

COURSE AND PROGNOSIS

The mortality rate of SJS-TEN depends on the severity of the disease and the quality of medical care; it is low for SJS (1 percent)[12] and ranges from 5 to 50 percent in TEN. The following factors appear to be unfavorable prognostic signs: old age,[121] extensive skin lesions, neutropenia,[122,123] impaired renal function, and intake of multiple drugs.[15] Septicemia (*Pseudomonas aeruginosa*, *Staphylococcus aureus*, gram-negative, and *Candida albicans*), gastrointestinal hemorrhage, pneumonia, and fluid and electrolyte imbalance leading to renal insufficiency are the major complications leading to death.[89,124] Recovery is slow and depends on adequate treatment; healing may require from 3 to 6 weeks or more, depending on extent and severity of the lesions and presence of complications (e.g., superinfection). New crops of lesions may arise for days to weeks in cases caused by long-acting drugs. Healing occurs with a great tendency for scar and stricture formation at mucosal sites. Recurrences are the exception rather than the rule, but do occur if the inciting drug is taken again. In these cases, the severity of symptoms may undergo a drastic crescendo.

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CHAPTER 60

John R. Stanley

Pemphigus

DEFINITION AND CLASSIFICATION

The term *pemphigus* refers to a group of autoimmune blistering diseases of skin and mucous membranes that are characterized histologically by intraepidermal blisters due to acantholysis (i.e., separation of epidermal cells from each other) and immunopathologically by the finding of in vivo bound and circulating IgG directed against the cell surface of keratinocytes. The nosology of this group of diseases is outlined in Table 60-1. Essentially pemphigus can be divided into three major types: vulgaris, foliaceus,[1] and paraneoplastic.[2] In *pemphigus vulgaris* the blister occurs in the deeper part of the epidermis, just above the basal layer, and in *pemphigus foliaceus*, also called superficial pemphigus, the blister is in the granular layer. Although the blisters in paraneoplastic pemphigus and pemphigus vulgaris are at the same level of the stratified squamous epithelium, paraneoplastic pemphigus is distinguished by unique clinical, histologic, and immunologic features.[2]

Pemphigus vulgaris and pemphigus foliaceus are the originally characterized, classic forms of pemphigus. Individual patients have either one or the other type of pemphigus and rarely cross from one type to the other, although this crossover has been reported in unusual cases.[3] However, within each type of pemphigus is represented a spectrum of disease. Various points along these spectra have been given unique names, but the presentation of these diseases is fluid, and patients' disease, over time, will usually cross these artificial designations. Thus, patients with pemphigus vulgaris may present with more localized disease, one form of which is called pemphigus vegetans of Hallopeau. This may become slightly more extensive and may merge into pemphigus vegetans of Neumann. Finally, with more severe disease, full-blown pemphigus vulgaris may appear. Similarly, patients with pemphigus foliaceus may