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Life-Threatening Dermatoses

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Four life-threatening dermatoses—Stevens-Johnson syndrome, toxic epidermal necrolysis, Kaposi's varicelliform eruption and purpura fulminans—are unique in their abrupt onset and rapid progress to death, but prompt diagnosis and proper therapy can often cure the condition or prevent undesirable sequelae. Since two of the four conditions can follow the use of a variety of drugs and all may be secondary to an infectious agent, any physician may encounter them in practice and should be aware of their seriousness.

MODERN THERAPY has so changed the course of many fatal dermatoses, such as pemphigus vulgaris, that now patients may die from the complications of therapy rather than from the disease itself. In dermatoses such as generalized exfoliative dermatitis, where etiologic factors may be obscure, the cause of death is frequently difficult to assign, although in some patients it may be high output cardiac failure, particularly in those with underlying heart disease.[1]

A discussion of all the potential life-threatening dermatoses is beyond the scope of this paper and many represent the cutaneous component of a more serious systematic disease, as in systemic lupus erythematosus, dermatomyositis, periarteritis nodosa, and malignant atrophic papulosis of Degos. There are also several fatal congenital disorders such as epidermolysis bullosa letalis, as well as certain serious mycobacterial and fungal infections.

This discussion is limited to four different and distinct life-threatening dermatoses: Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), Kaposi's varicelliform eruption (KVE) and purpura fulminans. These four are unique in that they are always abrupt in onset and can swiftly progress to death. Most important, prompt diagnosis and proper therapy can often cure the condition or prevent undesirable sequelae.

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Stevens-Johnson Syndrome

Stevens-Johnson syndrome is usually classified as a serious variant of bullous erythema multiforme.[2] It ordinarily affects children and young adults. Its abrupt onset is heralded by high fever, headache, painful erosions about the lips and in the mouth, and bilateral conjunctivitis (Figures 1 and 2). A vesiculo-bullous eruption, often with the typical iris or target lesion, develops on the skin (Figure 3). The course is stormy, with many signs of toxicity, and bronchial pneumonia may develop as a complication. The death rate in patients with this syndrome is 10 to 25 percent.[3]

Mucosal lesions occur in all patients, regardless of the severity, and this finding, plus the typical cutaneous lesions, should make the diagnosis readily apparent. Serious ocular involvement is a dreaded complication since it can result in partial or total blindness.[4] Duration of the disease is

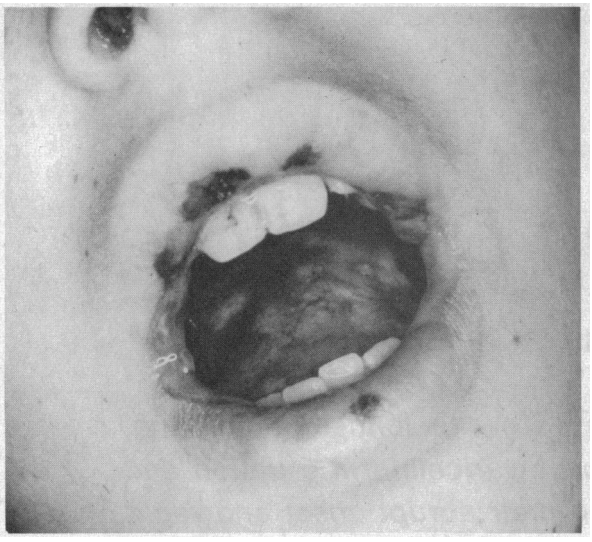

Figure 1.—Erosive lesions of lips and tongue in patient with Stevens-Johnson syndrome.

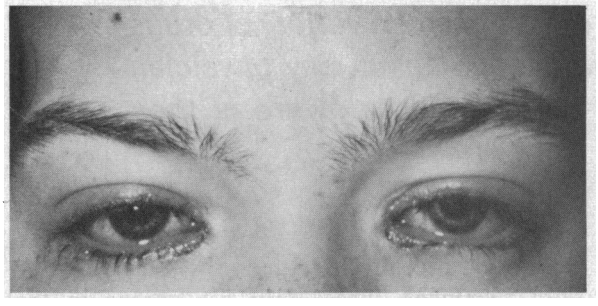

Figure 2.—Bilateral conjunctivitis in patient with Stevens-Johnson syndrome.

ordinarily four to six weeks but severe cases may last two or three months.

Stevens-Johnson syndrome may occur in association with systemic infection, pregnancy, foods, deep x-ray therapy, and neoplasms.[5] Of the viruses herpes simplex and adenoviruses are the most frequent causative agents.[6] It is also probably the most common severe drug eruption, with a great number of drugs implicated—penicillin, sulfonamides, antipyrine, phenylbutazone, the anticonvulsants and others. The most frequent etiologic drugs are reported to be the long-acting sulfonamides, especially sulfamethoxypyridazine.[2] Mounting evidence in recent literature also indicates that the mycloplasma organisms are not infrequent causative agents. Ludlam and associates[7] found raised titers of complement fixative antibody to mycoplasma in four out of five cases of Stevens-Johnson syndrome; and Lyell and associates[8] isolated mycoplasma pneumonia from blister fluid and material from the throats of patients with erythema multiforme.

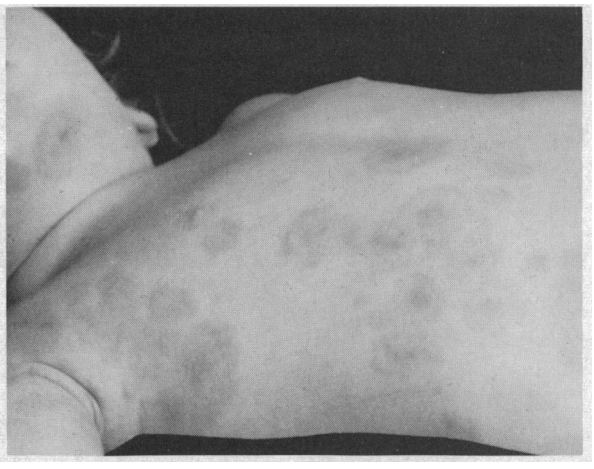

Figure 3.—Target lesions of erythema multiforme as seen in Stevens-Johnson syndrome.

Treatment consists of prompt admission to hospital, nursing care, systemic corticosteroids and the use of broad spectrum antibiotics, especially if mycoplasma infection is discovered. Significant eye involvement requires ophthalmologic consultation and the topical use of corticosteroids. Even with massive doses of corticosteroids, new lesions may appear and the disease may worsen. Renal involvement with hematuria or even renal tubular necrosis has been reported, and these conditions may progress to renal failure.[9,10]

Toxic Epidermal Necrolysis

Toxic epidermal necrolysis (TEN) first became recognized as a distinct entity after Lyell's description of the disease in 1956.[11] Lyell used the word *toxic* to express the acute damage to the epidermis. Since 1956 about 400 cases of this syndrome have been reported and an analysis of them reveals that the disease has many causes and variable prognosis.[12] The typical clinical description and course of the disease in the young is exemplified by the following case:

The patient, a three-year-old boy, first became ill in January 1967 and his mother noted the sudden onset of redness about the face and trunk in association with exquisite tenderness of the skin. He had had a low-grade fever for the previous 24 hours, for which the mother had given aspirin tablets, totaling approximately four. Within a few hours the erythema progressed about the face and became especially pronounced in the flexural skin areas. The scalp remained uninvolved. The patient was admitted to the hospital two days after onset of the illness, at which time he was anorectic and in distress from painful skin. Desquamation had

begun in the areas of the upper back and the Nikolsky sign was present. Except for the skin changes and a few blisters about the lips, no abnormalities were noted on physical examination and there was no elevation of temperature. Leukocytes numbered 4,800 per cu mm with normal differential except for 8 percent eosinophils. Hemoglobin content and results of urinalysis were normal as were cultures of the blood and throat. Nasal cultures revealed coagulase-positive Staphylococcus aureaus, phage type 71.

The child was admitted to isolation and reverse isolation and high doses of penicillin were started. Intravenous fluids were given for the next three days since painful blisters about the lips and mouth prevented oral ingestion. By the third hospital day definite desquamation of the epidermis from the most erythematous areas of the back, chest, ears, neck and hands had begun (Figures 4 and 5). The pain, erythema and facial edema improved decidedly after only 24 hours of treatment, and by the fifth hospital day the condition was resolving rapidly. The child was discharged from the hospital on the eleventh day completely well and with only mild erythema of the previously desquamated areas. He remained free of disease on follow-up examinations.

This is the typical history of a young patient with TEN. The characteristic features are the abrupt onset, exquisite skin tenderness, erythema which is most pronounced on the face and flexural areas, typical burn-like desquamation (hence the term "scalded skin syndrome"), and the usual 10- to 14-day course with complete recovery.[13] A short prodrome of malaise, lethargy and fever may precede the disease, but once the erythema appears the disease becomes explosive. When death occurs it is usually within the first five to eight days. Laboratory investigations of the blood are usually not informative although leukocytosis and leukopenia have both been reported.[14] Histologically there is necrosis of the superficial layers of the epidermis with a striking absence of inflammation.[11]

A symposium on TEN was held in Munich in November 1969.[15] From the reports given, it is clear that there are many causes of the syndrome and that the condition in children shows many differences from that in adults. In the adult type, components of Stevens-Johnson syndrome are frequently associated both histologically and clinically and indeed not only can differential diagnosis be difficult but both syndromes may occur

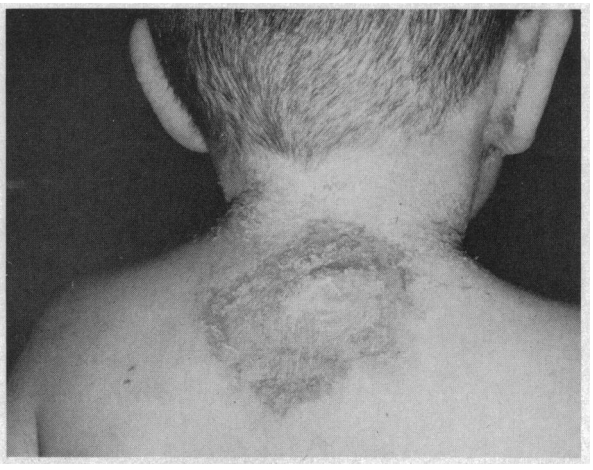

Figure 4.—Desquamation and suppuration from areas of previous erythema and tenderness (TEN).

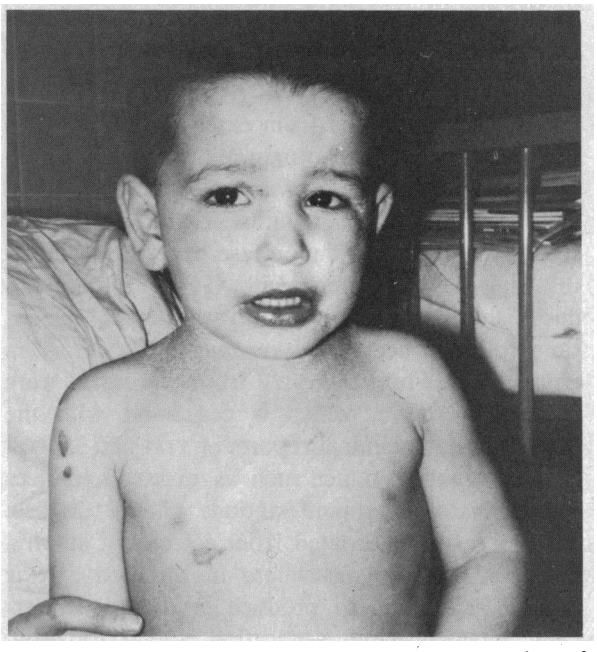

Figure 5.—Patient with TEN on third hospital day of therapy.

in the same patient at the same time. I recently observed such a patient whose eruption was secondary to administration of ampicillin.

The childhood variety of TEN is thought to be due in almost all instances to infection of the skin, throat or elsewhere with staphylococcus Group 2, phage type 71, thus linking this disease with Ritter's disease of the newborn.[13,16,17] The childhood variety has now been referred to as Ritter von Rittershain-Lyell's disease.[17] The syndrome in children can be caused by other bacteria, however, and is thought by some investigators to be a rare manifestation of the exanthems.[13]

Arbuthnott and associates[18] showed that the

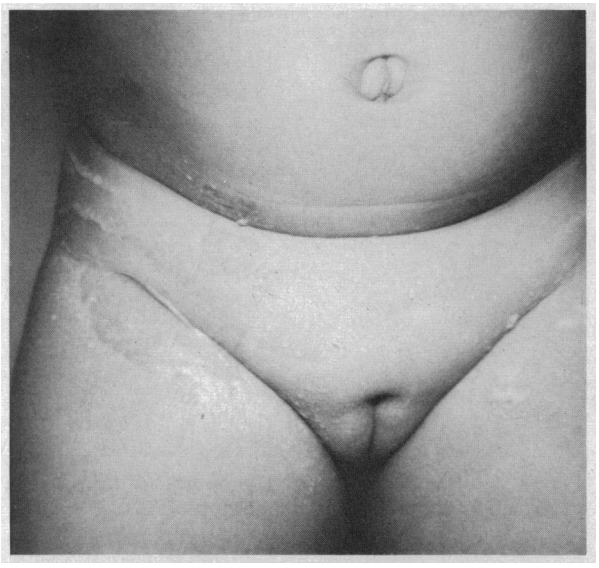

Figure 6.—Localized areas of TEN in a child treated with sulfadiazine for an upper respiratory infection.

staphylococci isolated from cases of TEN produce a major identifiable exotoxin not present in staphylococci isolated from cases of impetigo. Melish and Glasgow[19] and Arbuthnott and associates[20] recently reproduced the disease experimentally by injecting newborn mice with Group 2 staphylococci isolated from cases of TEN. The characteristic exfoliation occurs only in mice less than seven days of age. Fluid aspirated from the bullae were repeatedly sterile, which is consistent with the observations in clinical reports of TEN and suggest that a soluble product such as exotoxin induces the dermatologic manifestations of the disease. This factor is elaborated from a focus of staphylococcus infection elsewhere in the body. It is then disseminated to produce erythema, tenderness, intraepidermal separation and exfoliation. It was also found that the newborn mice had an inadequate inflammatory response to the effective doses of staphylococci and this appears to provide optimum conditions for the growth of bacteria and the production of the toxin. The nature of the soluble blister-producing substance has not yet been defined but it is non-dialysable and is thermolabile, suggesting that it is a macromolecular product of Staphylococcus aureus and not a metabolite of small molecular weight.[20] In the experimental model, as well as apparently in humans, susceptibility to this necrolytic factor seems to decrease with age.

Recurrences of TEN in children are unusual, the outlook is good, mortality rate is low and complications few.[13] The desquamation that follows the uncommon entity of staphylococcal scarlet fever is probably a mild example of TEN.[21] Minor, localized, necrolytic skin reactions can also occur after the use of drugs and may be overlooked (Figure 6). In such cases the reexposure to the offending drug may evoke the disease, with serious sequelae. Other less common causes of the disease in children are immunizations and boric acid intoxication.[16]

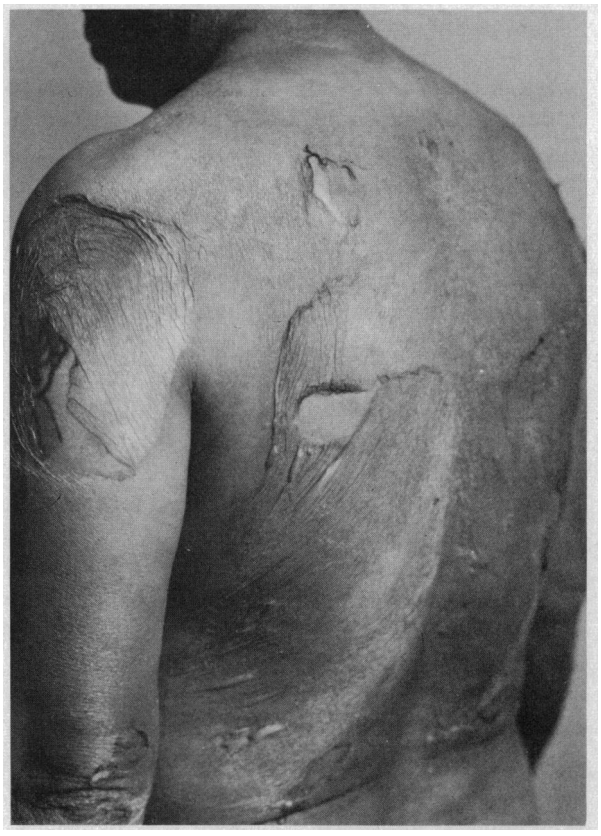

Figure 7.—Large areas of desquamation (TEN) in a patient following drug therapy. Patient died of the disease after a second exposure to the offending drug. (Patient seen at U.S.P.H. Hospital, San Francisco)

The adult variety of TEN is in many instances due to drugs, the most frequent etiologic agents being phenylbutazone, anticonvulsants, and the sulfonamides[16] (See Figure 7). Recurrences are common in adults, especially if the offending drug is given again. In drug-induced TEN, little is known about the pathophysiology, but it does not seem to be a manifestation of either the Sanarelli-Shwartzman reaction or the Arthus phenomenon.[15] There is also an idiopathic form of the disease which occurs especially in middle-aged women and carries a mortality rate of 50 percent.[15] Adult patients with this idiopathic form are also prone to recurrent attacks should they survive the initial

episode. Schuppli,[22] collecting reports of 314 cases of TEN from the literature between 1962 and 1968, found an overall mortality rate for adults of about 40 percent. As indicated, the best prognosis appears to be in the childhood variety, although in children less than one year of age the mortality rate has been reported to be 33 percent.[13]

The prognosis of TEN is to a large extent dependent upon adequate nursing care. The patient should be nursed in as aseptic conditions as possible, and general treatment should follow the rules of burn therapy. Birke and associates[12] recently successfully treated five patients with advanced manifestations of TEN in an atmosphere of warm, dry air throughout the acute phase. This treatment appears to eliminate the need for topical antibacterial therapy. Systemic antibiotics are essential in the childhood cases secondary to Staphylococcus aureus and are often indicated in adults. The role of corticosteroid therapy is not yet clear but some investigators are of the opinion that corticosteroids given in high doses early in the course of the disease are of definite therapeutic benefit.[12,13,22]

Kaposi's Varicelliform Eruption

Kaposi's varicelliform eruption (KVE) is an acute viral infection superimposed upon chronic dermatosis. Either the herpes simplex virus or the vaccinia virus is the etiologic agent and, depending upon the causative virus, the infection is designated either eczema herpeticum or eczema vaccinatum. More recently the Coxsackievirus A16 was implicated as another possible cause of the disease.[23] The underlying dermatitis is most commonly atopic eczema but the disease can occur in seborrheic dermatitis, Darier's disease, ichthyosis, contact dermatitis, pemphigus, acne, scabies, impetigo, secondary syphilis and in the Wiscott-Aldrich syndrome.[24-27] KVE is the main reason to avoid smallpox vaccinations in patients with eczema or a past history of eczema, eczema affecting a household member, or any active skin disorder. Clinically the lesions and symptoms produced by the herpes simplex are often indistinguishable from those of the vaccinia virus, but the history of exposure and laboratory studies can aid in differentiation. This differentiation is often of great importance, not only as to the choice of therapy but as to prognosis also, since herpes simplex, once established, can be recurrent whereas vaccinia without further exposure is not. Recurrent attacks of KVE due to herpes simplex virus tend to be less severe than the primary episode and may occur on atopic skin after the eczema has disappeared.[28]

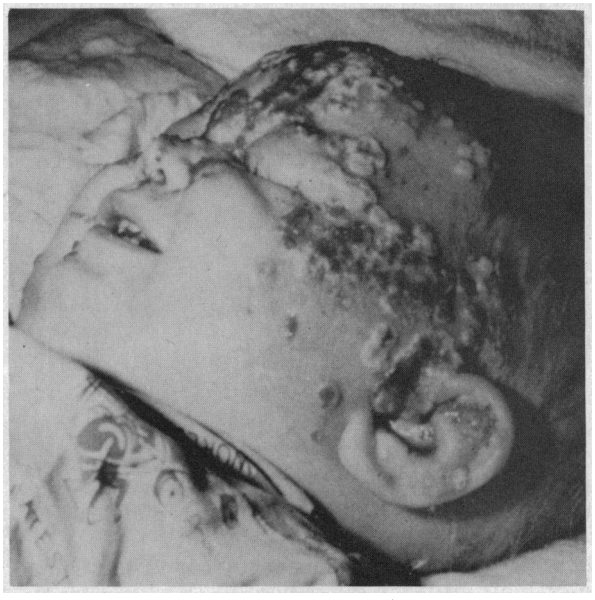

Figure 8.—Eczema vaccinatum

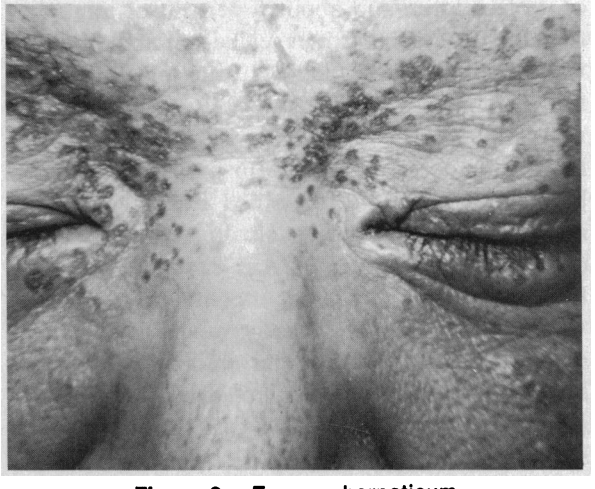

Figure 9.—Eczema herpeticum

The vesicles appear abruptly as a succesion of crops both in and about the diseased skin and they continue to erupt over a period of a week. The vesicles frequently become confluent and pustular and regional lymphadenopathy appears (Figures 8 and 9). Ocular keratitis is a frequent complication, especially when the face is involved. Fever and toxic symptoms may occcur and in the extensive case the patient is seriously ill. Viremia with viral infection of internal organs accounts for some of the fatalities as does secondary bacterial septicemia.[29]

Recent surveys show that about 125 cases of

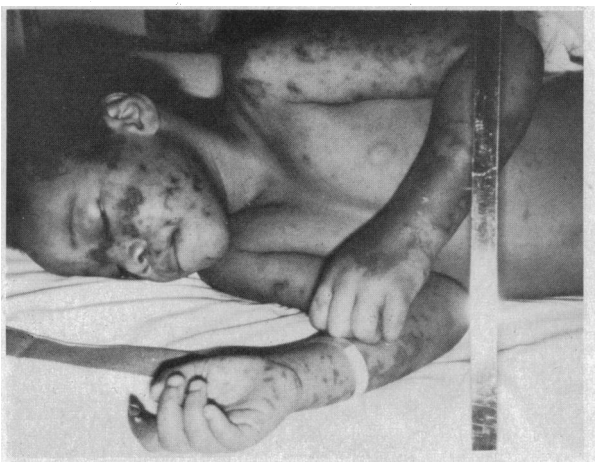

Figure 10.—Multiple areas of purpura 48 hours after onset of purpura fulminans. (From: Cram and Soley.[42])

eczema vaccinatum occur each year in the United States, usually in patients with atopic eczema.[30] Eczema vaccinatum used to be fatal in 30 to 40 percent of children and about 6 percent of aduts before the development of vaccine immune globulin (VIG).[31] Epidemics occurred after mass vaccination campaigns, as in May 1947 when 43 cases were reported in New York City alone.[32] VIG is hyperimmune gamma globulin prepared from the blood of United States Armed Forces personnel recently vaccinated against smallpox and is distributed by American Red Cross centers across the United States. The present recommended dose of VIG is 0.6 ml per kg of body weight given intramuscularly in divided 10 ml amounts every four hours until total dosage is achieved.[33] It has significantly reduced mortality in children, as was shown in a recent study by Kempe of 132 cases, in which the death rate fell to 7 percent.[34] VIG theoretically terminates viremia and prevents further spread of skin lesions by producing neutralizing antibodies which otherwise appear late in the eczema vaccinatum patient.

The thiosemicarbazones, antiviral compounds reported successful in the treatment of cases of variola and severe vaccinal complications, may eventually prove to be the therapeutic drugs of choice.[35] Methisazone, a thiosemicarbazone drug, has not yet been approved for marketing in the United States but is available for general use in Great Britain. It is given orally with an initial loading dose of 200 mg per kg of body weight followed by 400 mg per kg in divided doses over a total of 48 hours. The most prominent side effects are nausea and vomiting, which may be partially controlled by the use of antiemetics.[35,36]

Eczema herpeticum can be more difficult to treat. The administration of gamma globulin in amounts to provide sufficient levels of neutralizing antibodies immediately after onsent of the primary herpetic infection has been used to try to prevent viremia and systemic spread of the virus, but this has been of little value once the infection is established or in recurrent disease.[28] Wet compresses and the use of antibiotics in the event of secondary infection are the primary forms of therapy. Idoxuridine (Dendrix,® Herpex® or Stoxil®) should be used in the eyes if herpes keratitis appears.[37] I have also used idoxuridine on the skin in cases of eczema herpeticum, with significant benefit.[38] Prevention is the best therapy for KVE, especially in the case of eczema vaccinatum, where more careful screening of patients for the known contraindications to vaccination should be stressed.

Purpura Fulminans

Purpura fulminans is a severe, rapidly fatal illness which occurs most often in the young.[39] The disease is characterized by the abrupt appearance of large areas of cutaneous hemorrhage and gangrene during the convalescent period of various bacterial and viral infections. Intravascular occlusions with ischemia and localized areas of massive ecchymosis are associated with chills, fever, prostration and rapid progression to hemorrhagic shock, coma, and finally death. In the cases reported more than 90 percent of the patients died and the survivors usually lost digits or limbs during the process.[40,41] In this disease, more than any of the others, prompt diagnosis and adequate therapy is paramount to saving life. This is exemplified by the following case, which was previously reported elsewhere.[42]

The patient, a five-year-old Negro girl was admitted to hospital on 14 February 1967 with a 48-hour history of fever, myalgia, listlessness and generalized progressive purpuric skin eruption. Diagnosis before admission was meningitis, and the patient had been given aqueous penicillin 1,000,000 units intravenously, hydrocortisone, sulfadiazine and intravenous fluids. Because of shock she had also been given a blood transfusion and intravenous levarterenol (Levophed®). On admission she was extremely ill. Bilateral conjunctival hemorrhage, edema of face and extremities, and wide areas of ecchymosis were noted (Figure 10). Leukocytes numbered 15,400 per cu mm with a

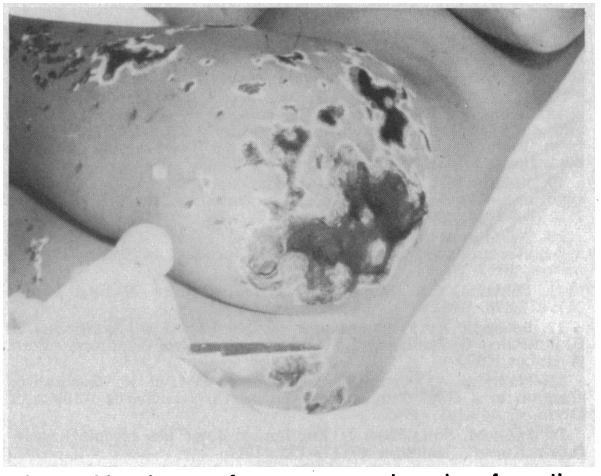

Figure 11.—Areas of gangrene and eschar formation in patient with purpura fulminans.

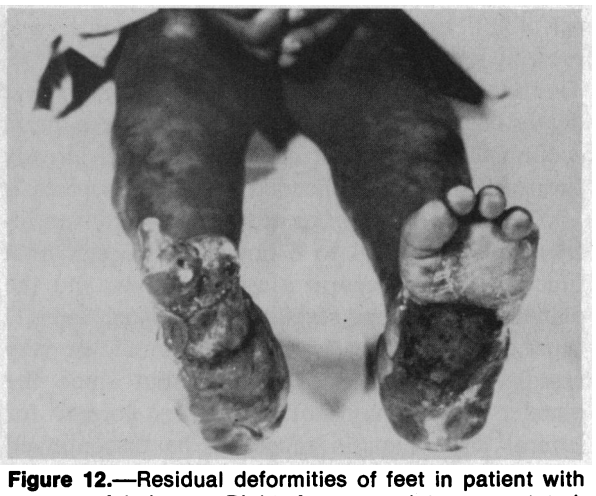

Figure 12.—Residual deformities of feet in patient with purpura fulminans. Right foot was later amputated. (From: Cram and Soley.[42])

shift to the left in the differential, and platelets 80,000. Bleeding time, partial thromboplastin and prothrombin time were prolonged. Results of spinal fluid examination were within normal limits and cultures of this fluid and the blood were negative.

A diagnosis of purpura fulminans was made and treatment was started immediately with heparin. The penicillin and hydrocortisone were continued and the child was also treated with 250 ml of low molecular weight dextran on the first, third and fifth day. Over the next 48 hours many of the ischemic areas improved and the patient became more responsive. Large bullae appeared over many of the purpuric areas, as well as gangrene of several digits and the less viable ecchymotic skin (Figure 11). By the seventh hospital day the child was decidely improved and the leukocyte and platelet counts and prothrombin time had returned to normal. The heparin and dextran were stopped and careful daily debridement of the necrotic skin areas was begun. On 9 March 1967 the patient was transferred to a plastic surgery service for further corrective operation. She underwent six operations for debridement with skin grafts to the left forearm, both legs and both feet. Amputation of the right foot was later necessary (Figure 12).

The cause of purpura fulminans has not been fully established but the presence of perivascular inflammation and intravascular thrombosis has prompted most observers to consider it analogous to the generalized Shwartzman phenomenon which can be experimentally demonstrated in laboratory rabbits.[43,44] The primary pathologic event in the affected person is disseminated intravascular coagulation (DIC), the hemostatic hallmarks of which are the depletion of platelets, fibrinogen, prothrombin, factor V, factor VIII and the activation of the fibrinolytic enzyme system.[45] McKay also demonstrated the appearance of an anticoagulant (antithrombin) in purpura fulminans.[46]

Many infectious organisms and disease states have been associated with DIC.[47] One of the fundamental biological properties of certain viruses is their ability to trigger the blood-clotting mechanisms *in vivo*.[48] Probably minor degrees of intravascular clotting occur in several viral disorders such as varicella, rubella and rubeola, but only on very rare occasions does the explosive and life-threatening form of purpura as described herein occur. McKay emphasized that DIC may be quite extensive or severe without the development of occlusive thrombi.[48] DIC may also follow bacterial septicemia, the prototype of which is meningococcemia. Here, however, the skin purpura rarely results in extensive necrosis, mucous membrane bleeding is common and signs of meningitis plus positive blood and spinal fluid cultures for the meningococcus are the diagnostic features.

Until rather recently most patients with purpura fulminans were treated with a combination of anticoagulants, antibiotics and corticosteroids,[49] and occasionally low molecular weight dextran was used.[50] Since a fundamental pathogenic mechanism of purpura fulminans is DIC, anticoagulants such as heparin are now the therapeutic agents of choice.[48] The beneficial effect of heparin is exerted through its antithrombin activity and direct prevention of further thrombosis. The therapeutic

use of anticoagulants has been life-saving in several recently reported cases of purpura fulminans.[41,45,51] Treatment must be begun promptly since most deaths occur in the first 48 to 72 hours and heparin sodium does not affect capillary thrombi already formed.[45] The recommended dosage of heparin is 100 units (1 mg) per kg of body weight given intravenously every 4 to 6 hours until coagulation functions in preheparin plasma samples and the platelet counts have stabilized to normal levels.[51] Most of the hemostatic mechanisms recover very rapidly, often within 48 hours, but since the platelet count may not return to normal for several days, heparin must not be discontinued prematurely.

Since necrotic lesions resembling purpura fulminans are seen in other conditions not involving intravascular clotting, a diagnosis of consumption coagulopathy must be reliably confirmed before heparin is given.[52] In hospitals not having facilities for complete coagulation study, minimum studies should include a platelet count and determination of plasma prothrombin, partial thromboplastin and thrombin clotting times.[51]

Epsilon-amino-caproic acid has been recommended for the latter phases of this disease[48,52] but the role of fibrinolysis in purpura fulminans and thus the use of this agent that inhibits fibrinolysis is not well defined as yet. More studies are needed before the value of this other therapeutic agent can be adequately assessed.

REFERENCES

1. Voigt GC, Kronthal HL, Crounse RG: Cardiac output in erythrodermic skin disease. Am Heart J 72:615-620, 1966

2. Rostenberg A, Fagelson HJ: Life-threatening drug eruptions. JAMA 194:660-662, Nov 8, 1965

3. Carroll OM, Bryan PA, Robinson RJ: Stevens-Johnson syndrome associated with long-acting sulfonamides. JAMA 195:691-693, Feb 21, 1966

4. Ashby DW, Lazar T: Erythema multiforme exudativum major (Stevens-Johnson syndrome): Lancet 1:1901-1095, 1951

5. Fitzpatrick TB, Arndt KA, Clark WH, et al: Dermatology in General Medicine. McGraw-Hill, Inc, 1971, pp 599-600.

6. Strom J: Febrile mucocutaneous syndrome (Ectodermosis erosiva plurioficialis, Stevens-Johnson syndrome, etc.) in adenovirus infection. Acta Dermatovener (Stockholm) 47:281, 1967

7. Ludlam GB, Bridges JB, Benn EC: Association of Stevens-Johnson syndrome with antibody for mycoplasma pneumoniae. Lancet 1:958-959, 1964

8. Lyell A, Gordon A, Dicks HM, et al: Mycoplasmas and erythema multiforme. Lancet 2:1116-1118, 1967

9. Comish JS, Kerr DN: Erythema multiforme and nephritis. Brit Med J 2:84-88, 1961

10. Blufarb SM, Szanto P: Erythema multiforme associated with acute renal tublar necroses. Arch Derm 92:367-372, 1965

11. Lyell A: Toxic epidermal necrolysis: Eruption resembling scalding of skin. Brit J Derm 68:355-361, 1956

12. Birke G, Liljedahl S-O, Rajka G: Lyell's syndrome—Metabolic and clinical results of a new form of treatment. Acta Dermatovener (Stockholm) 51:199-209, 1971

13. Lowney ED, Baubles JU, Kreye GM, et al: The scalded skin syndrome in small children. Arch Derm 95:359-369, 1967

14. Bailey G, Rosenbaum JM, Anderson B: Toxic epidermal necrolysis JAMA 191-979,982, 1965

15. Bandman HJ, Braun-Falco O: Das Lyell-Syndrome. Bern, Stuttgart, Vienna, Hans Huber, 1970

16. Lyell A: A review of toxic epidermal necrolysis in Britain. Brit J Derm 79:662-671, 1967

17. Koblenzer PJ: Acute epidermal necrolysis (Ritter von Rittershain-Lyell)—A clincopathologic study. Arch Derm 95:608-617, 1967

18. Arbuthnott JP, Gemmell CG, Kent J, et al: Haemolysin and enzyme patterns of coagulase-positive staphylococci isolated from toxic epidermal necrolysis, Ritter's disease and impetigo contagiosa. J Med Microbiol 2:479-487, 1969

19. Melish ME, Glasgow LA: The staphylococcal scalded-skin syndrome—Development of an experimental model. N Engl J Med 282:1114-1424, 1970

20. Arbuthnott JP, Kent J, Lyell A, et al: Toxic epidermal necrolysis produced by an extracellular product of Staphylococcus aureus. Br J Derm 85:145-149, 1971

21. Feldman, CA: Staphylococcal scarlet fever. N Engl J Med 267:877-878, 1962

22. Schuppli R: Prognose und therapie des Lyell-Syndroms. *In* Braun-Falco O, Bandman HJ (Ed S): Das Lyell-Syndrome. Bern, H Huber, 1970

23. Nahmias AJ, Froeschle JE, Feorino PM, et al: Generalized eruption in a child with eczema due to Coxsackievirus A16. Arch Derm 97:147-148, 1968

24. Jank M, Soltz-Szots J: Zur immunologie des eczema herpetiforme Kaposi, Hautarzt 17:173-175, 1966

25. Hitselberger JF, Burns RE: Darier's disease—Report of a case complicated by Kaposi's varicelliform eruption. Arch Derm 83:425-429, 1961

26. Silverstein EH, Burnett JW: Kaposi's varicelliform eruption complicating pemphigus foliaceus. Arch Derm 95:214-216, 1969

27. Doeglas HMG, Molhuysen TMG: Kaposi's varicelliform eruption. Arch Derm 100:592-595, 1969

28. Wheeler CE, Abele DC: Eczema herpeticum, primary and recurrent. Arch Derm 93:162-173, 1966.

29. Monif GRG, Brunell PA, Hsiung GD: Visceral involvement by herpes simplex virus in eczema herpeticum. Am J Dis Child 116:324-327, 1968

30. Lane JM, Ruben FL, Neff JM, et al: Complications of smallpox vaccination 1968—National surveillance in the United States. N Engl J Med 281:1201-1208, 1969

31. Copeman PW, Wallace HJ: Eczema vaccinatum. Brit Med J 2:906-908, 1964

32. Fries JH, Borne S, Barnes HL: Varicelliform eruption of Kaposi due to vaccinia virus complicating atopic eczema. J Pediat 32:532-542, 1948

33. Conn HF: Curent Therapy 1970, Philadelphia, WB Saunders Co., 1970, p 63

34. Kempe CH: Studies on smallpox and complications of smallpox vaccination. Pediatrics 26:176-189, 1960

35. Bauer DJ: Clinical experience with the antiviral drug Marboran (1-methylesatin 3-thiosemicarbazone) Ann NY Acad Sci 130:110-117, 1965

36. The Medical Letter 13: No 19, Sep 17, 1971, p 78

37. Kaufman, HE, Martola EC, Dohlman EH: Use of 5-Ido-2-Deoxyuridine (IDU) in treatment of herpes simplex keratitis. Arch Ophthal 68:235-239, 1962

38. Corbett MB, Sidell CM, Zimmerman M: Idoxuridine in the treatment of cutaneous herpes simplex. JAMA 196:441-444, May 2, 1966

39. Bouhasin D: Purpura fulminans. Pediatrics 34:264-270, 1964

40. Crawford SE, Riddler JG: Purpura fulminans. Pediatrics 34:264, 1964

41. Hjort PF, Rapaport SI, Jorgensen L: Purpura fulminans—Report of a case successfully treated with heparin and hydrocortisone. Review of 50 cases from the literature. Scand J Hemat 1:169, 1964

42. Cram DL, Soley RL: Purpura fulminans. Br J Derm 80:323-327, 1968

43. Stetson CA Jr: Studies on the mechanism of the Shwartzman phenomenon: Certain factors involved in the production of the local hemorrhagic necrosis. J Exp Med 93:489, 1951

44. Glass RD: Purpura gangenrosa—Report of a case, with a discussion of the Shwartzman phenomenon. Med J Aust 2:300, 1962

45. McKay DG, Margarettin W: Disseminated intravascular coagulation in virus diseases. Archs Intern Med 120:129, 1967

46. McKay GF, Pisciotta AV, Johnson SA: Hemostatic mechanisms, antithrombin III and purpura fulminans. Am J Clin Path 38:357-366, 1962

47. Yoshihawa T, Tanaka KR, Guze LB: Infection and disseminated intravascular coagulation. Medicine 50:237-258, 1971

48. McKay DG: Pathology, diagnosis and therapy of disseminated intravascular coagulation. Proc Roy Soc Med 61:1129-1134, 1968

49. Becker FT, Buckley RP: Purpura fulminans associated with varicella. Arch Derm 94:613-618, 1966

50. Patterson JH, Pierce RB, Anderson JR, et al: Dextran therapy of purpura fulminans. N Engl J Med 273:734, 1965

51. Antley RM, McMillan CW: Sequential coagulation studies in purpura fulminans. N Engl J Med 276:1287-1290, Jun 8, 1967

52. Rodriguez-Erdmann F: Bleeding due to increased intravascular blood coagulation. N Engl J Med 273-1370-1378, 1965