TOXIC EPIDERMAL NECROLYSIS (TEN): A short review with report of five cases.

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TOXIC EPIDERMAL NECROLYSIS (TEN): (Short Review)

Toxic epidermal necrolysis (TEN) was first described by Lyell in 1956[1]. TEN is the most severe blistering disease with a mortality ranging between 20-66% and an incidence of 1.3/million/year in France[2], Germany[3] and Italy[4].

TEN is caused by drugs in 89% of cases and comprises 1% of skin drug reactions that require hospitalization[5]. Drugs implicated in TEN are sulphonamides 34%, anticonvulsants 18%, nonsteroidal anti-inflammatory drugs 18%, allopurinol 3.6% and miscellaneous drugs 26.4%. More than 100 drugs including polio vaccine, DPT and methotrexate were reported to cause TEN[6,7,8].

Less than 5% of patients give no history of drug intake and this group may be related to infection. The incidence of TEN among HIV patients is 1/1000/year reflecting an inherent high risk of reaction and more exposure to sulfonamide[6]. TEN was also reported in 9 patients after bone marrow transplantation and seems to be related to acute Graft Versus Host Disease (GVHD)[9]. Food additives, fumigants and contact with chemicals have been also implicated in few cases of TEN[7].

TEN affects all ages and is rare in early infancy with poor prognosis[10] and females are affected more than males with a ratio varying from 3:2 to 2:1[7].

The interval between drug intake and the onset of TEN was estimated to be 1-4 days rather than 10-14 days[11], while others estimated this interval to be 1-3 weeks or may be 48 hours in patients who had history of similar reactions to the drug[12].

The criteria for diagnosis of TEN are:[11,13, 14].

1. Fever and explosive onset of morbelliform or confluent erythematous rash with bullae or erosions covering 20% or more of the body surface without preceding target lesion. The rash is associated with pain, soreness and tenderness
2. Sudden onset and mucous membrane affection with widespread skin lesions within 24-48 hours.
3. Peeling of areas of the skin more than 3 square centimeters.
4. Exclusion of staphylococcal scalded skin syndrome.
5. Histopathologic picture suggestive of TEN.

There are common features shared by TEN, bullous erythema multiforme (EM) and Steven Johnson Syndrome (SJS). It is questionable whether they are different diseases or variants within a continuous spectrum. Bastuji et al[14] tried to clear this vagueness and found that mucosal lesions are present in 90% of patients in all groups and there was no relation between the extent of mucosal affection and the epidermal detachment. Bastuji et al[14] classified the group into five subgroups according to the individual skin lesions and the extent of the surface area affected as in the following table:

Definitions of Individual Lesions:

1. Typical target is usually acrally located, characteristically seen post herpetic, is usually less than

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	Area affected with Detachment	Typical/ Target	Atypical Target	Spots
Sub Group 1 Bullous E.M.	< 10%	+	Raised	-
Sub group 2 SJS	< 10%	-	Flat	-
Sub group 3 Overlap SJS and TEN	10 - 30%	-	Flat	-
Sub group 4 TEN with spots	> 30%	-	Flat	-
Sub group 5 TEN without spots	> 10%	-	-	-

3 cm in diameter, has regular round shape, has well defined border and has atleast 3 different zones (central disk surrounded by 2 concentric rings the innermost of which is palpable, oedematous and paler than the disk).

2. Raised atypical target is round oedematous palpable lesion with 2 zones and poorly defined border.

3. Flat atypical target is round poorly defined, not palpable and made of 2 zones.

4. Spots appear as macules, red or purpuric, not palpable, irregular in shape and size and confluent with blisters on all or part of them.

5. Epidermal detachment usually progresses over a period of few days.

The clinical manifestation of TEN:

TEN begins by a prodromal stage of 2-3 days or one day to 3 weeks. In the prodromal stage the patient gets signs and symptoms of upper respiratory tract infection; fever, anorexia, rheinitis, sore throat, cough, conjunctivitis and difficult micturation.

The prodromal stage is followed by the acute phase which lasts from 8-12 days. During the acute phase fever persists and mucous membranes are affected especially conjunctivae, oral, pharyngeal, tracheal, bronchial, nasal, anal, vaginal and urethra with urine retension. The skin lesions begin as burning, red, tender and painful eruption which usually begins on the face and upper body and spreads caudally[7] but predominates on the trunk and proximal part of the limbs. The skin shows large flaccid bullae, sloughing of the epidermis and positive Nicolsky's sign in large areas and at sites of adhesive plaster or ashesive electrodes. The rash generally spreads rapidly and reaches maximal extension in 2-3 days and sometimes few hours and one in seven patients will get 100% loss of epidermis in less than 24 hours but the scalp was never affected[7]. Donor site and grafted skin were spared from necrolysis in a patient with TEN[16]. To explain the localization of lesions in TEN it is suggested to be due to innate differences in the properties of the skin from different parts of the body[16]. One such difference is that in TEN as well as in pemphigus and pemphigoid there is regional variation in expression of skin antigens which are targets of the immune reaction[17]. Another possibility is variable expression of cell surface molecules such as intercellular adhesion molecule-1 (ICAM-1) which is thought to play a role in traffiking of lymphocytes to the epidermis. Localized misregulation of ICAM-1 may influence localization of lesions in fixed drug eruption[19].

TEN in the acute stage has to be differentiated from Staphylococcal scalded skin syndrome, Toxic

shock syndrome, Kawasaki disease, Second degree burn, Generalized fixed drug eruption and S.J.S.

The acute phase is followed by a recovery phase which takes 1-2 or 3-4 week[12,7] during which mucous membranes and skin re-epithelialize even while the disease is still spreading to the lower limbs. No scarring occurs except in areas of pressure or infection. The thorax regenerates in few days while flexures and back heal more slowly. The mucous membranes take longer time and the glans penis may need 2 months to heal.

Complication & Sequelae[12,7]

1. Fever is high and persistant, sudden drop rather than rise of temperature is more indicative of infection. Impaired thermal regulation may occur.

2. Skin infection, nail dystrophy and nail loss, hypohidrosis and dermal dessication, scarring alopecia, hypo or hyper pigmentationthat may improve by time and may persist for more than 10 years.

3. Mucous membrane affection:

a) Gastrointestinal tract: chronic mouth erosion, xerostomia, oesophageal bleeding and stricture, dysphage, profuse protein rich diarrhoea leading to increased fluid loss and hypo albuminemia, severe chronic diarrhoea may occur and may require intestinal resection, overt hepatitis may occur in 10% of patients. Acute pancreatitis may occur with increase in serum amylase and serum lipase.

b) Respiratory complications occur in 30% of patients such as mucous retension, erosion and sloghing of tracheo-bronchial mucosa which when aspirated leads to shallow breathing, atelectasis, pneomonitis and pneumonia. Interstitial oedema due to increased alveolar capillary permeability and 10-20% of patients may need artificial ventilation.

4. Occular complications may occur in up to 50% of patients and these are:

a) conjunctivitis which may lead to pseudomembrane formation,

b) Photophobia,

c) Ectropion, entropion, trichiasis and symblepharon,

d) Vascularization of the cornea, corneal opacities, ulceration and scarring.

e) Lacrimal duct destruction and chronic dry eye,

f) Conjunctival destruction with fusion of the eye lids to one another and to the globe leading to blindness.

5. Fluid loss: an adult with 50% of the body surface affected looses 3-5 liters of fluid from the skin with 40 grams of protein in each liter with electrolyte loss in the same concentration as in plasma. The fluid loss leads to hypokalaemia and kidney failure.

6. Blood: Normocytic hypochromic anaemia, lymphopenia, neutropenia which is seen in 30% of patients and is a poor prognosticsign, thrombocytopenia in 15% of patients, disseminated intravascular coagulopathy from release of lysosomal enzymes by sepsis.

7. Sepsis: Infection by staph aureus or pseudomonas aerogenosa may spread from skin and cause septicemia and septicaemic shock which is fatal. Central catheters and venous lines promote infection.

8. Kidneys may rarely show glomerulo nephritis, pre renal azotaemia and tubular necrosis.

9. Increased energy expenditure

a) Hypermetabolic state produced by IL-I. Hypermetabolism is twice the basal metabolic rate when 50% or more of the body surface is affected.

b) Environmental temperature below 25°C increaeses the hypermetabolic state.

c) In an adult protein loss from skin surface and hypercatabolism may lead to protein loss upto 150- 200 grams per day.

d) Inhibition of insulin secretion and or insulin resistance in peripheral tissue lead to glucosurea which leads to increased aminoacid break down which will cause more calory and fluid loss.

10. Miscellaneous: a) Hypovolemia; b) Hypoxic injury to the brain from hypotension; c) Gastrointestinal haemorrhage; d) Pulmonary emboli; e) Sjogren syndrome; f) Urinary tract infection; g) Chronic erosion of genitalia and phymosis; h) Abnormal liver function.

Mechanisms leading to TEN

History of an offending drug is obtained in 70-90% of cases of TEN. It is suggested that there is a genetic predisposition to TEN evidenced by the increased association with HLA B12 and HLA DR4 found when HLA-A; B and DR typing were done in 44 survivors of TEN[10]. The susceptibility to severe drug reaction may be related to different HLA antigens for different kinds of drugs. Most patients with TEN have an unusual metabolism of the offending drug leading to an increased production of reactive metabolites. It is possible that there is a linkage between HLA genes and gene or genes responsible for metabolism of the drug. It is suggested that the drug reactive metabolites behave as a hapten and adhere to carrier proteins on the membrane of epidermal cells thus inducing an immune response mediated by lymphocytotoxic reaction causing epidermal necrosis. Direct evidence for immunologic mechanism in TEN is lacking but there are factors that supports immune mediated reaction and these are: the drug may act as a hapten and the immune response to it depends on HLA phenotype[20]; the association of TEN with GVHD suggests that TEN may be produced by cellular immune reaction; the occasional presence of drug dependant anti-epidermal anti bodies and the occasional appearance of post TEN Sjogren syndrome[20]. There is no evidence of complement activation or involvement of cytotoxic antibody reaction in the epidermal destruction[7]. The interleukin released and other cytokines contribute to fever and other symptoms or the fever may be due to a pyrogen produced by epidermal necrosis([20]. The tumor necrosis factor alfa secreted by activated macrophages may play a role in necrolysis of epidermis. Blisters found in TEN show predominance of activated CD8 positive T cells, and these cells were found to be cytotoxic[21]. The keratinocytes express HLA DR antigen possibly secondary to interferon gamma secreted by activated T cells[22]. Langerhans cells are reduced in number. The peripheral blood shows lymphopenia[23,24,12] with profound depletion of CD4 positive T lymphocytes possibly due to redistribution of these cells from blood to the dermis.

Pathophysiology[7,11,25]

Early lesions show in the papillary dermis moderate CD4 positive lymphocytes and CD8 positive lymphocytes at the dermo-epidermal junction. The basal cell layer shows hydropic and vacuolar degeneration and intercellular oedema. Effector dendritic CD8 positive T lymphocytes migrate to the epidermis where they react with the target keratinocytes. This interaction is mediated via microvillus processes and requires among other factors the presence of ICAM-I. This interaction results in a small increase of the intracellular calcium which flows through normal calcium transmembrane channel. This small increase in the intracellular calcium stimulates the pore forming transmembrane protein (Perforan) in the keratinocytes resulting in the formation of large transmembrane pores which allow massive influx of calcium from the extracellular compartment resulting in condensation of tonofilaments and nuclear fragmentation and isolated keratinocyt necrosis. After this stage the tumor necrosis factor alfa secreted by activated macrophages may contribute to the wide spread necrosis and detachment of the entire epidermis from a minimally altered dermis. The epithelial lining of sweat ducts become much more affected than those of the hair follicles. Direct immunoflourescence is always negative. Positive fluourescence around basal cell in two patients was once reported[26]. By electron microscopy lamina densa remain in the floor of the blisters. Necrotic cells with packed keratin are prominant in the basal cell layer. The electron microscopic (EM) findings suggest that a subset of T lymphocytes are involved in mediating cytolysis of target keratinocytes which are altered by a drug or its metabolites. By EM the keratinocytes appear necrotic and show nuclear disintigration and are opposed by dendritic cells which have the chromatin configuration of T lymphocytes. These keratinocytes also show membrane defects associated with cytoplasmic processes from the opposing lymphoid cells.[7]

Prognosis:

TEN is a disease of high mortality which may reach 60-70% and in a large series averaged 30%[27]. The factors which affect the prognosis of the disease are:- age, extent of necrolysis, exposure to many drug. It is estimated that each patient is exposed to an average of 4.4 drug([28]. Elevation of urea, creatinine, glucose, neutropenia[29], lymphopenia and

thrombocytopenia were linked with bad prognosis. Three of these mentioned prognostic factors are of paramount importance namely age, area of necrolysis and serum urea levels[27].

Treatment[30, 31, 32, 11]

1. Treatment should be in an intensive care or burn unit

2. Control of hypovolemia: 5-7 liters of fluids are needed in the first 24 hours - fluids are given by nasogastric tube and intravenous lines. Fluids given are water, electrolytes, plasma, albumin and macromolecular solutions as synthetic colloid.

3. Control of infection: Sepsis is the cause of death in more than 50% of cases. It is vital to control infection and it is recommended to do repeated skin culture from multiple sites daily, daily blood cultures, change of intravenous lines and urinary catheters, antiseptic baths, no antibiotic are to be given unless infection is proven.

4. Occular care daily by Ophthalmologist

5. Help of other specialities is requested whenever needed according to system affected.

6. Laboratory investigations are essential for diagnostic, prognostic and monitoring the disease and treatments.

7. Steroids are to be given early in the disease. They are important adjuvant treatment since they suppress the tumor necrosis factor alfa.

8. Plasmapheresis as a line of treatment is recommended since it removes the offending drug and its metabolites and eliminates necrolytic factors or inflammatory mediators.

9. Hyperbaric oxygen is given in a pressure chamber with pure oxygen at two atmospheric pressure for 60-120 minutes once daily. Re-epithelialization occurs after 10 days. This treatment activates dermal metabolism, enhances epidermal regeneration, has antishock effect, has antiseptic effect and is possibly immunosuppressive.

10. Cyclophosphamide (Cytoxan) is a derivative of nitrogen mustard: 75% of the drug is absorbed from gastrointestinal tract. It is mainly metabolized in the liver and its alkylating effect is exerted by its metabolites which are 50% protein bound. Fifty percent is excreted in urine and its half life is 2-10 hours. The recommended dose is 1-5 mg/kg/body weight/day and is best given in the morning with plenty of fluid to avoid cystitis and some prefer to give the drug on 3 divided doses. The side effects of cytoxan are: increased risk of lymphoma 5-40%, increased risk of bladder cancer, cardiomyopathy, pneumonitis, pulmonary fibrosis, haemorrhagic colitis, azospermia, anorexia, nausea, vomiting, stomatitis and alopecia (anagen)(5). Monitoring the drug is essential by doing basic CBC, the W.C. should not bè less then 3000/cu.mm and the granulocytes must be greater than 1000/cu.mm, CBC/ weekly. Urine analysis should be done daily and stop cytoxan if RBC appear in urine. Monthly blood biochemistry is recommended. Cytoxan produces dramatic response in TEN as it inhibits the cell mediated cytotoxicity.

Report of Five Cases:

In Hamad Medical Corporation (HMC) - Doha, Qatar - we shared in diagnosing and treating five patients suffering from TEN.

First Case:

An Indian boy (SSG) 2.5 year old was admitted to the Paediatric Department with fever (39.4C) and seizures. He weighed 14.5 Kg. and all his organs including skin and mucous membranes were normal. On 17.7.1994 he was given phenobarbital orally to control the febrile seizures. On 20.7.94 he became symptom free. On 21.7.1994 he became febrile again with cough. He was given I.V. ampicillin and cloxacillin because pneumonia was suspected. On 26.7.94 he became afebrile and antibiotics were discontinued. On 27.7.94 while still on phenobarb. the child had fever with red macular rash all over the body. On 5.8.94 the child was still febrile with rash, conjunctival injection, dry fissured lips and non tender cervical lymph nodes. Kawasaki disease was suspected and the child was given plus phenobarb I.V. gamma globulin and aspirin 100 mg/ kg body weight per day. On 6.8.94 fever persisted, the rash became brownish, wide spread with

palmoplantar erythema and blisters of hands, feet and mouth. SJS was suspected and phenobarb was discontinued. On 8.8.94 a dermatologist was consulted and TEN was diagnosed and confirmed by histopathology. The child had severe bilateral conjuctival injection, blistering of mouth and 95% of skin was scalded including the scalp with positive Nickolsky's sign (Fig. TEN 1-1, 1-2, 1-3, 1-4). On 8.8.94 child was transferred to Paediatric intensive care unit and cyclophosphamide was given I.V. 70 mg as drip over 60 minutes 8 hourly in the first day and 40 mg from the second to seventh day. The child received a total of 450 mg of cyclophosohamide combined with 1.5 mg dexamethasone I.V. 8 hourly in the first day then 1.5 mg once daily from second to seventh day thus receiving a total of 11.5 mg which is equivalent to 0.11 mg per Kg body weight per day. Other lines of care included 1) recording temperature, B.P., weight, respiratory rate and daily urinary output. 2) X-ray chest 3) Photography 4) Skin biopsy 5) Avoid hypothermia 6) rehydration by I.V. infusion 7) naso-gastric tube feeding 8) aseptic care to skin and I.V. line 9) eye, mouth and paediatric care 10) daily CBC, blood biochemistry, swab and culture, urine for routine and culture. On 11.8.94 he began to improve with peeling of skin and immediate re-epithelialization and on 16.8.94, he recovered completely without any complication (Fig. TEN 1-5, 1-6, 1-7, 1-8).

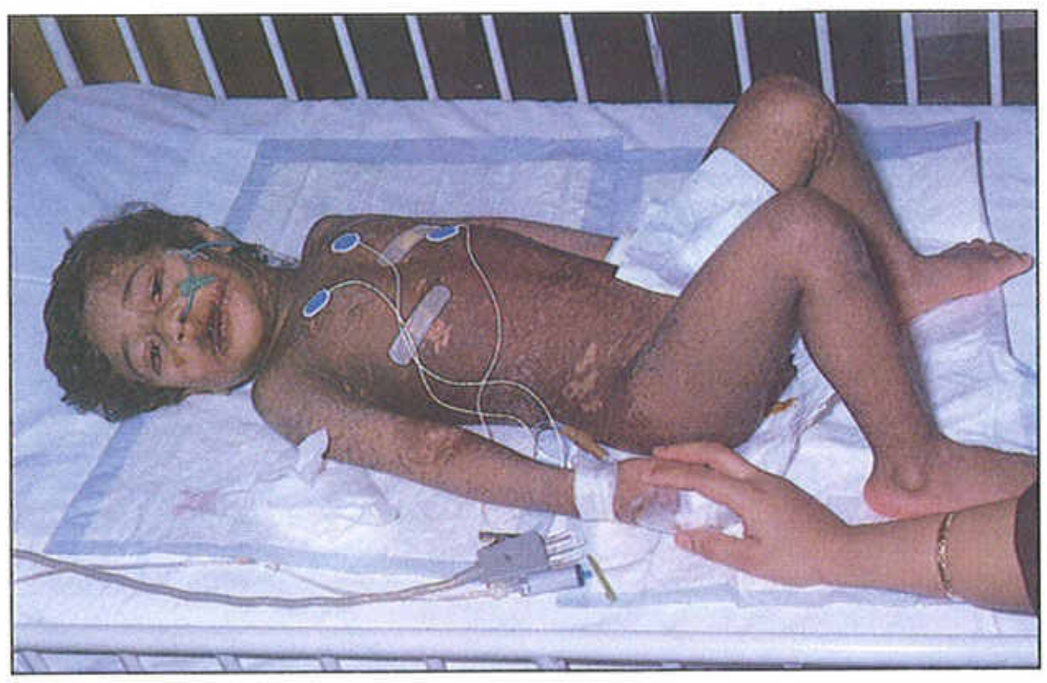

Fig. TEN 1-1 : 95% of skin is affected and looks scalded

Fig. TEN 1-2: Affection of eyes and mouth

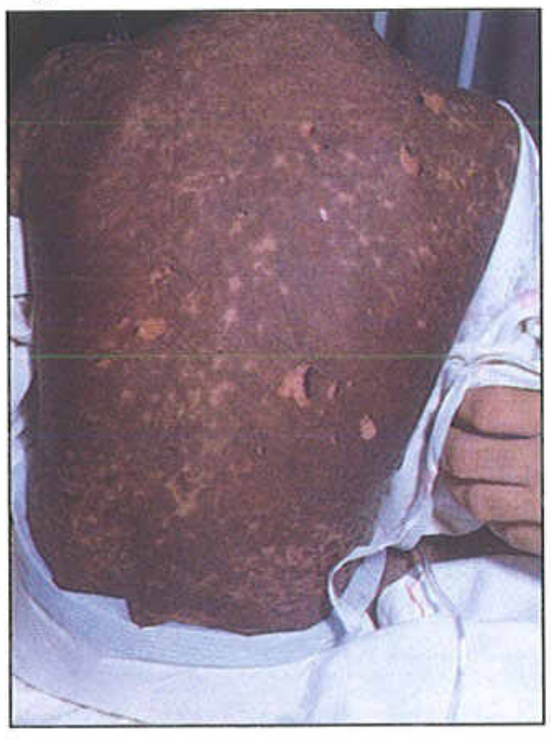

Fig. TEN 1-3: Close up view showing scalded skin and positive Nikolsky's sign

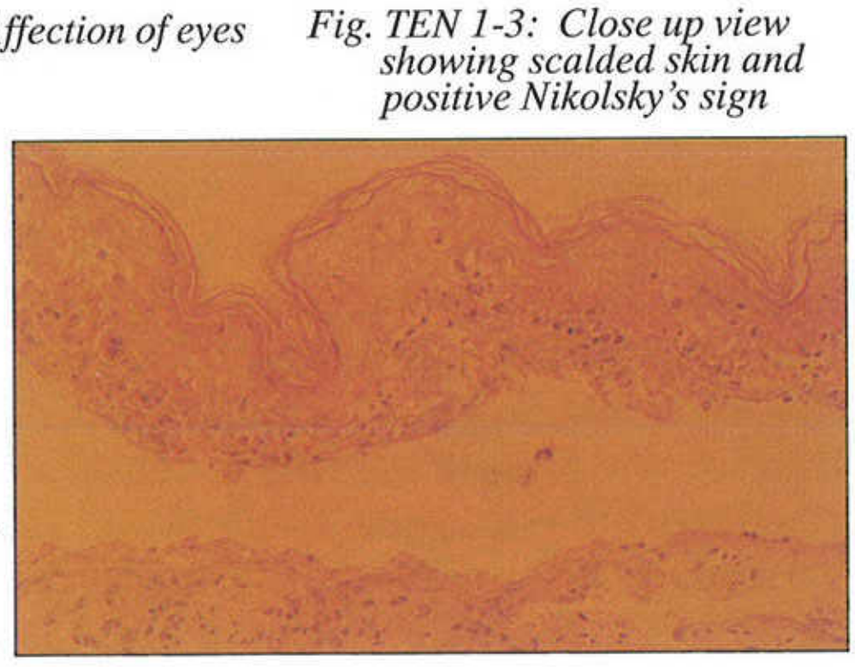

Fig. TEN 1-4: Histopathology with supra basal separation - sub-basal separation is also seen.

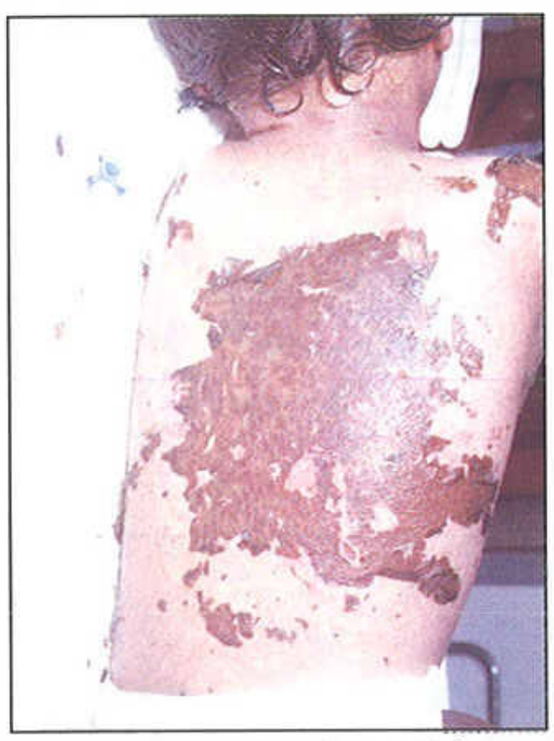

Fig. TEN 1-5: Pealing of skin with immediate reepithelialization

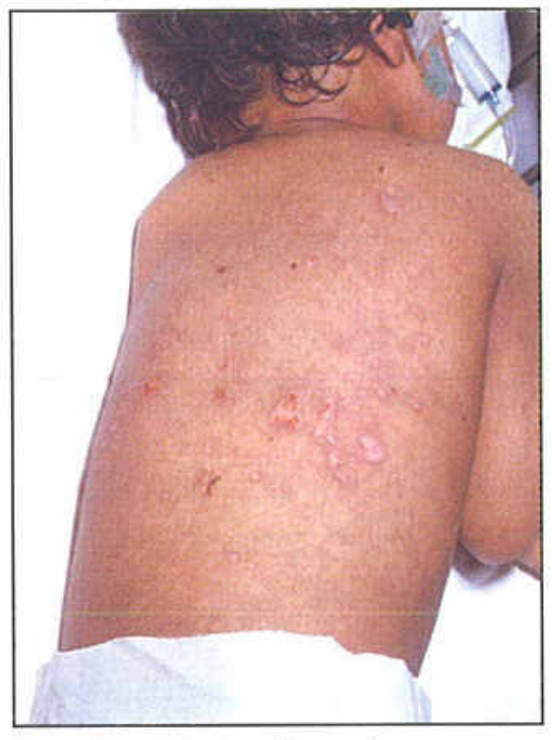

Fig. TEN 1-6: Complete cure showing back

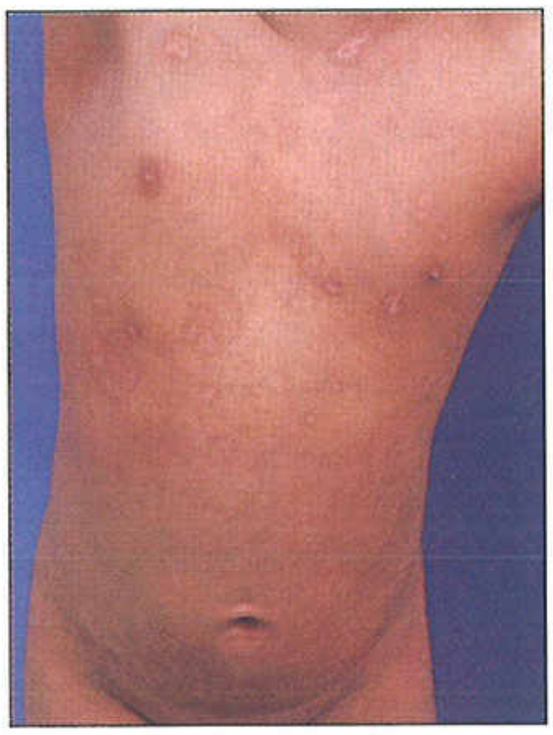

Fig. TEN 1-7: Complete cure showing front

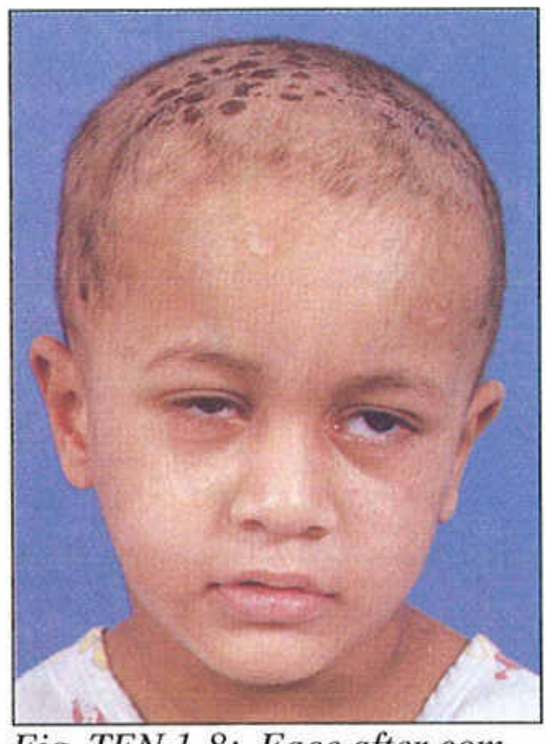

Fig. TEN 1-8: Face after complete cure - Note pealing of scalp skin

Second Case:

An Egyptian girl 6 years old (FMNS) was admitted to Paediatric Department on 10.6.95. She had psychomotor retardation since age of one year with intractable seizures since August 1992. She was maintained on anticonvulsants valproic acid for the past 3 years, Vegabatrin for the last one year and Lamactal for the past 20 days. On 4.6.95 she bacame febrile and on 6.6.95 developed generalized rash and parents suspected Lamactal to be the cause and discontinued it. On admission (10.6.95) she had fever 40C, generalized maculo-papular eruption on cheeks, auricular region, neck, upper limbs, trunk and lower limbs. The rash was confluent dark in colour with vesiculation and the lips were red and cracked and the paediatrician diagnosed drug reaction and started treatment with hydrocortisone I.V. On 11.6.95 a dermatologist diagnosed TEN confirmed by histopathology (Fig. TEN 2-1, 2-2, 2-3, 2-4). She was transferred to paediatric intensive care unit (PICU) on 11.6.95 and I.V. cyclophosphamide 70 mg plus 2.5 mg dexamethasone single dose were given daily for 7 days. She was nursed on the same basis as the first case and she improved daily and was cured 17 days after admission (Fig TEN 2-5; 2-6).

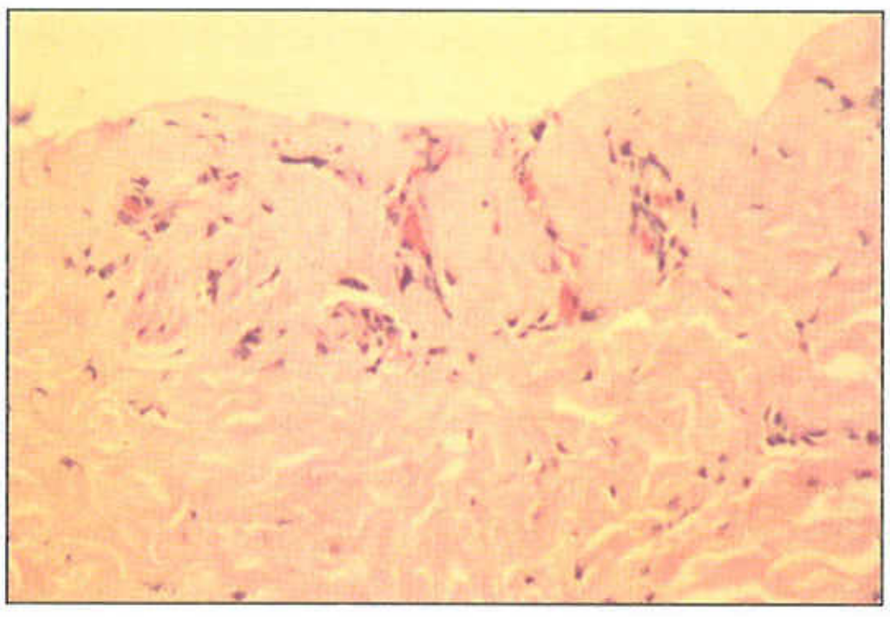

Fig. TEN 2-3: Complete lysis of epidermis with minimal dermal reaction

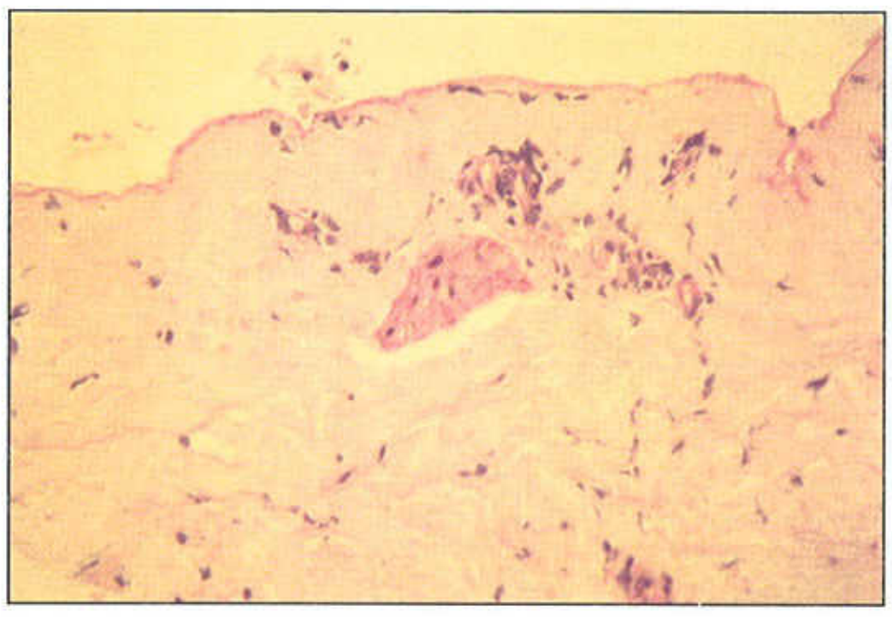

Fig. TEN 2-4: Basement membrane (PAS) at base of separation

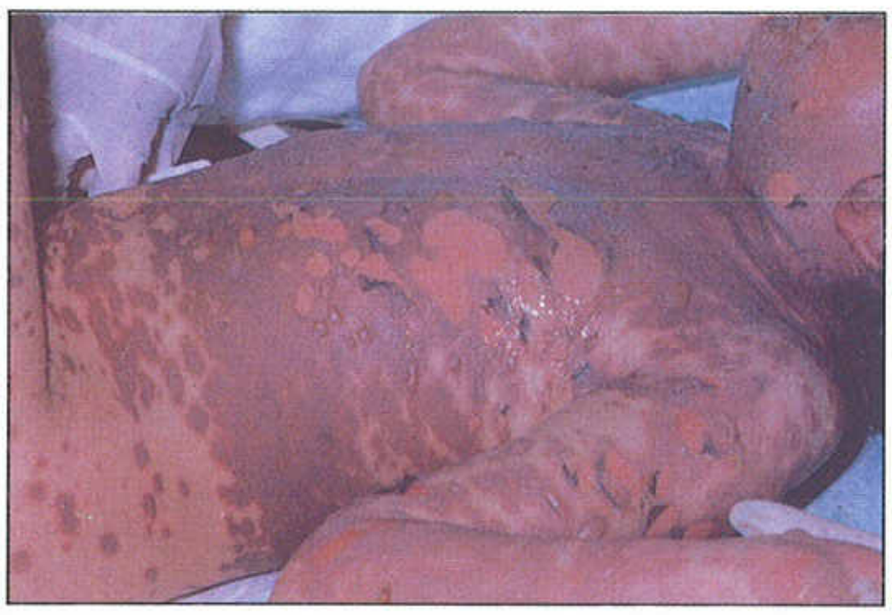

Fig. TEN 2-1: Affection of trunk and limbs

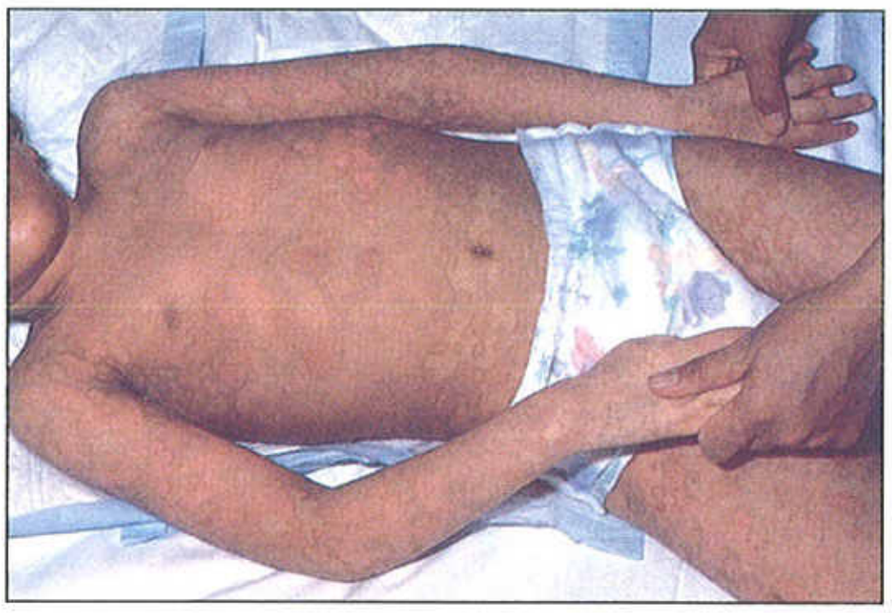

Fig. TEN 2-5: After cure

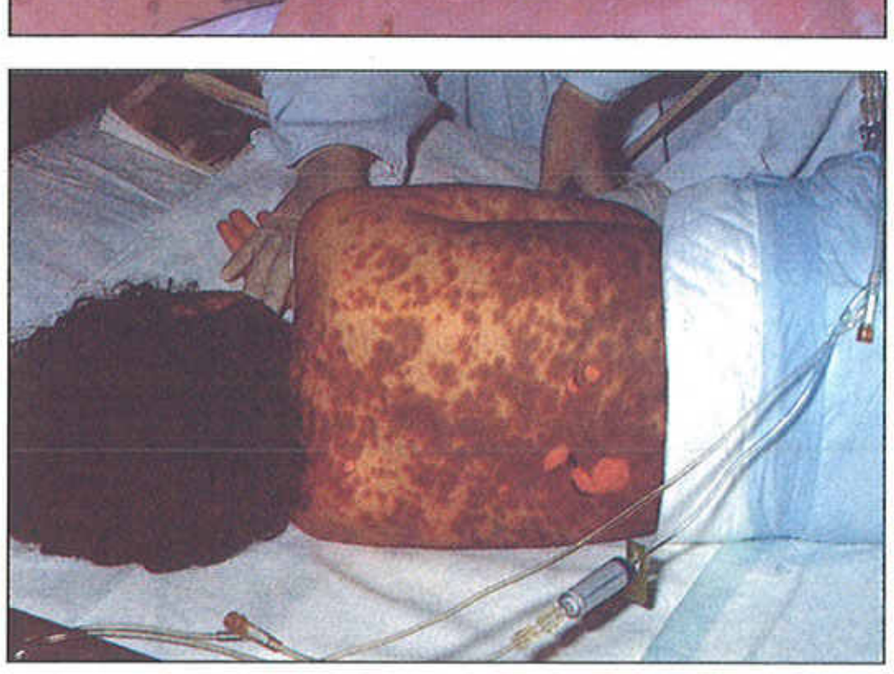

Fig. TEN 2-2: Affection of trunk and limbs

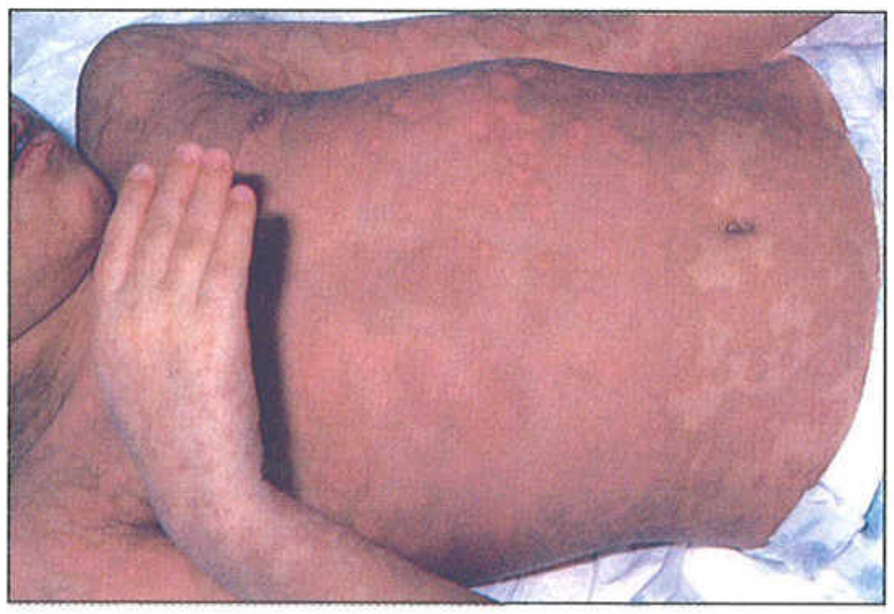

Fig. TEN 2-6: After cure

Third Case:

J.M.S. a 34 year old Indian epileptic male controlled on Tegretal and sodium valpoate. On 12.9.95 he suffered from fever. On 14.9.95 amoxicillin was given and on 15.9.95 he developed generalized rash. On 19.9.95 he was hospitalized because of fever 38.5 and rash diagnosed as SJS due to amoxicillin which was discontinued. Hydrocortisone 200 mg I.V. 8 hourly was given for 8 days during which the rash was increasing. On 26.9.95 a dermatologist opinion was requested. The patient had scalded skin affecting 100% of body surface including face, scalp, hands, feet and mouth. Histopathology confirmed the diagnosis of TEN. Fig. TEN 3-1, 3-2, 3-3, 3-4) Tegretal and sodium valpoate were discontinued and the patient was transferred to medical intensive care unit. On 26.9.95 cyclophosphamide was given 350 mg daily in a drip over one hour for 8 days and was combined simultaneously with dexamethasone 6 mg I.V. single daily dose. Patient was transferred from MICU to burn unit on 30.9.95 and sofratol dressing was done. On 7.10.95 he was completely cured and discharged on vegabatrim anticonvulsant. (Fig TEN 3-5, 3-6).

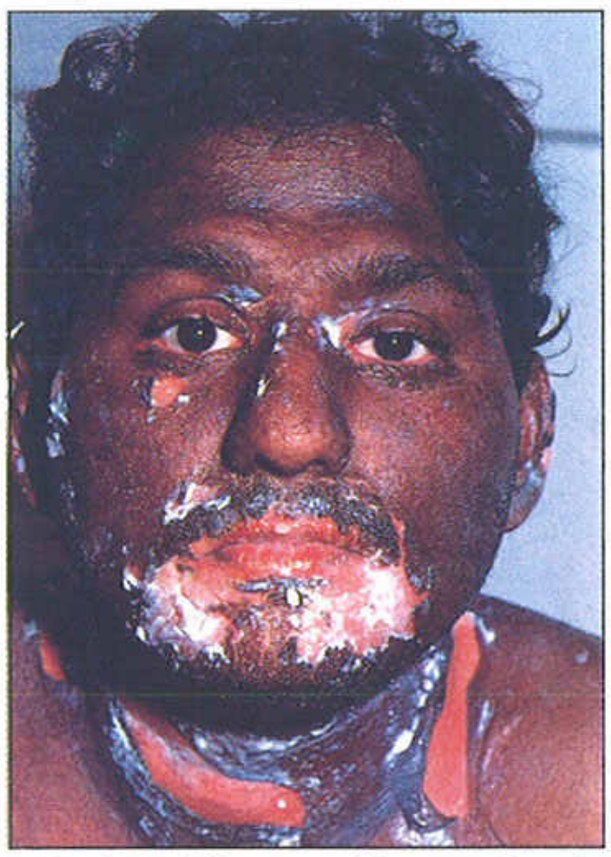

Fig. TEN 3-1: Affection of face and scalp

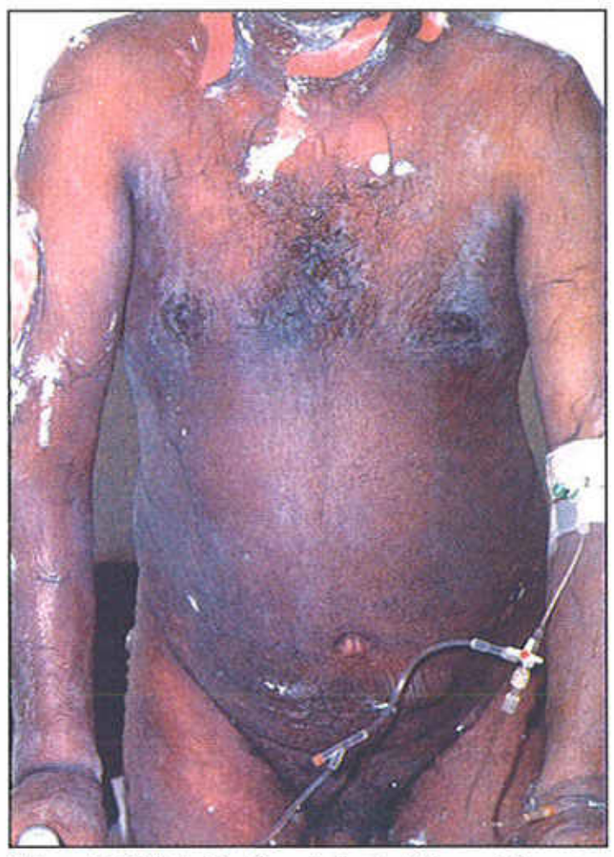

Fig. TEN 3-2: Scalded skin of front of trunk and limbs

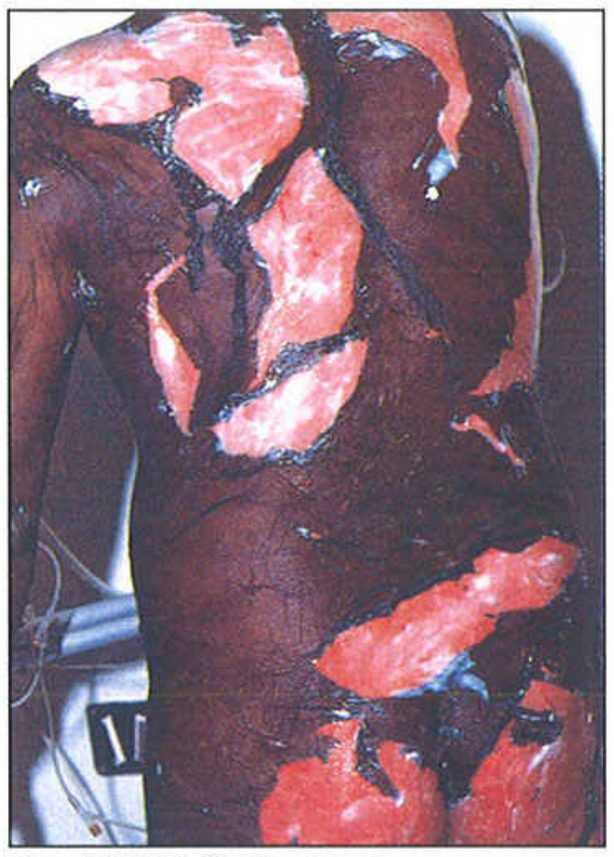

Fig. TEN 3-3: Scalded appearance of skin of back with positive Nikolsky's sign

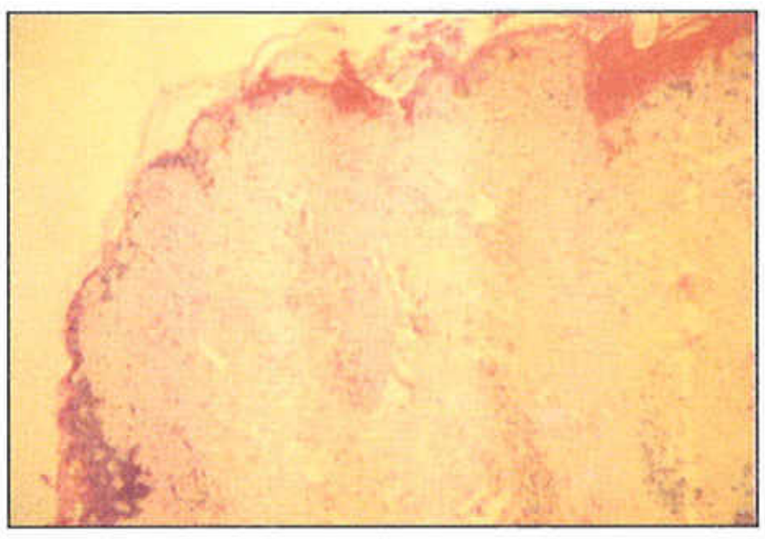

Fig. TEN 3-4: Sloughing of the epidermis with no dermal reaction

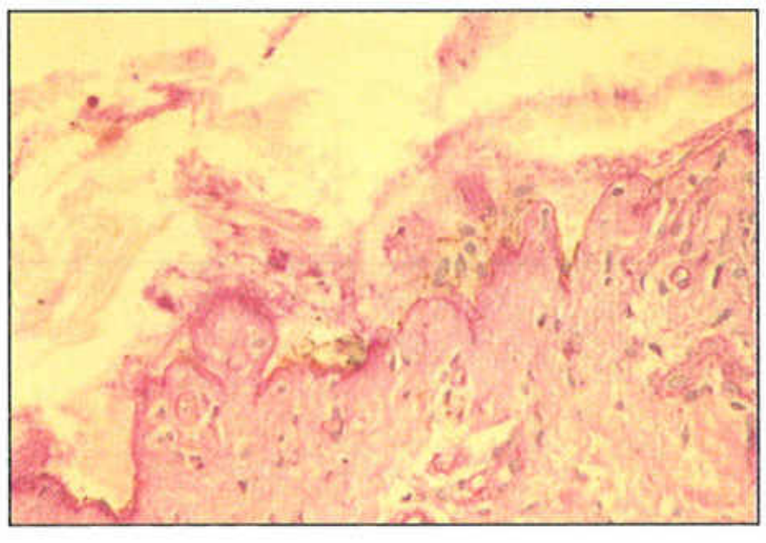

Fig. TEN 3-5: Basement membrane zone as shown by PAS at base of separation

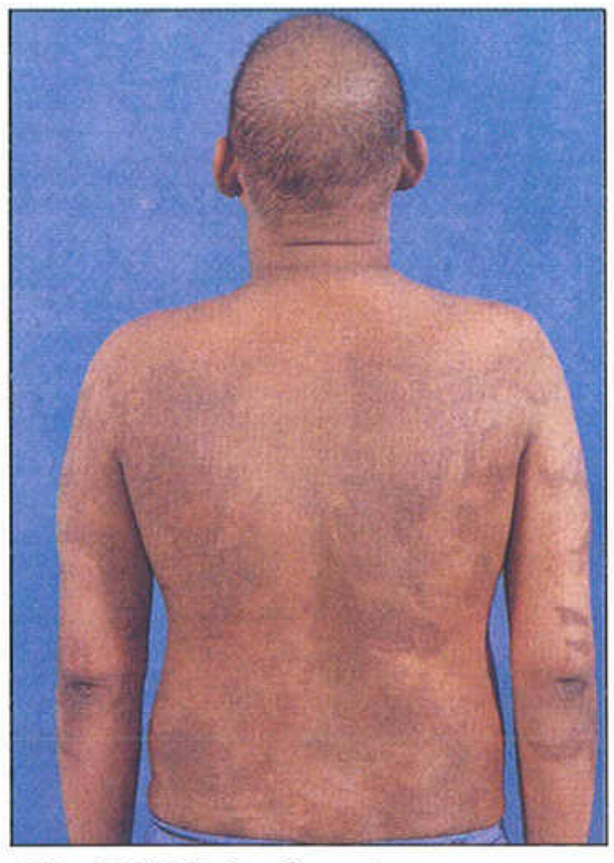

Fig. TEN 3-6: Complete cure

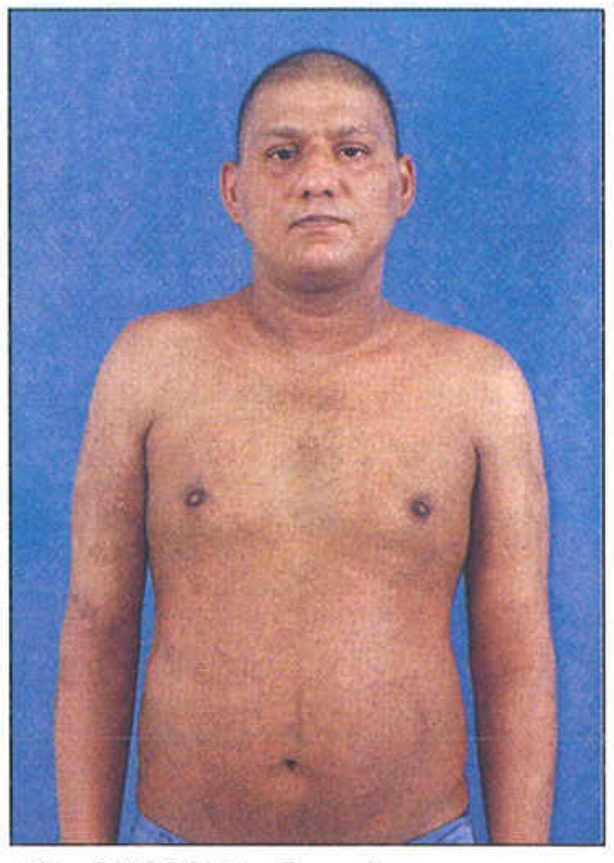

Fig. TEN 3-7: Complete cure

Fourth Case:

NSH a 33 years old Qatari female was admitted to ENT department on 19.1.96. She had fever, sore throat, pharyngeal oedema for 2 days. She took Brufen 2 days prior to the fever. She was seen by a dermatologist. She had confluent diffuse darkly erythematous rash mainly affecting limbs, trunk and face with soreness and redness of both palms and soles. The eyes and mouth were infected and the lips were darkly red and 30% of the body surface was affected. She was diagnosed to have an overlap of SJS and TEN. Patient refused biopsy and photography. I.V. 120 mg cyclophosphamide was given daily (2.5 mg/kg body weight/day) combined with 0.1 mg dexamethasone per kg. body weight per day for 5 day when she recovered with post inflammatory pigmentation of the trunk and limbs and was discharged on 30.1.96.

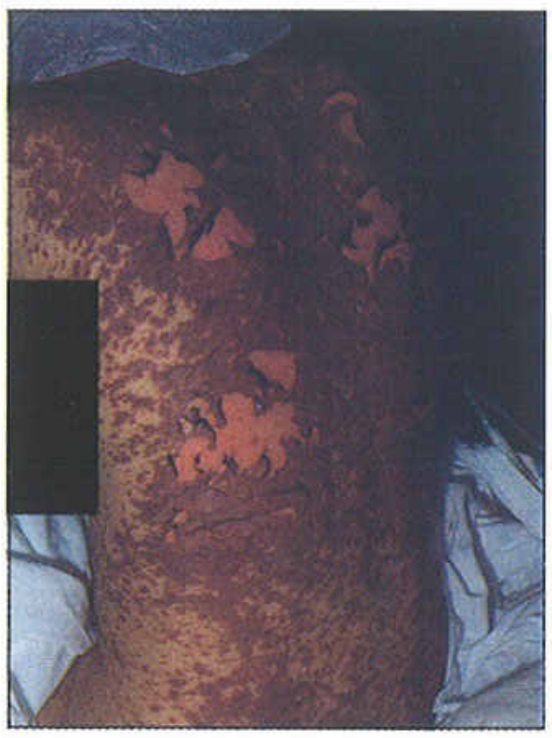

Fig. 5-1: Scalded appearance of skin of back with necrolysis.

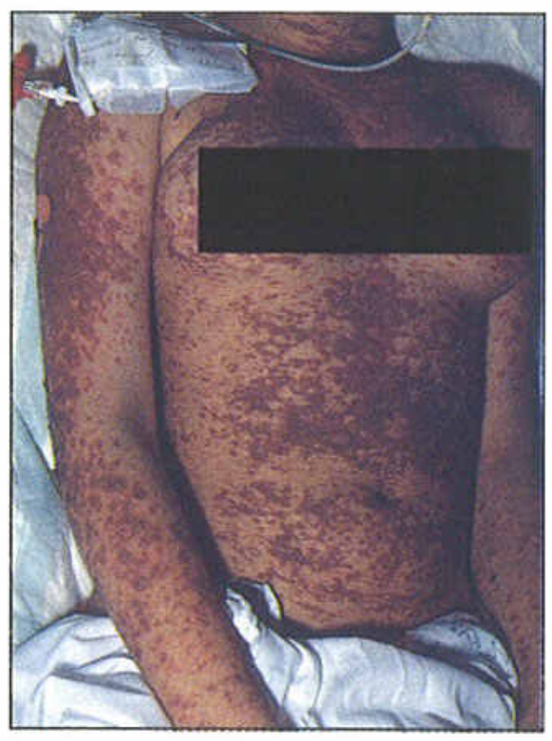

Fig. 5-2: Scalded appearance of skin of front trunk and upper limbs

Fifth Case:

(F.B.) a 14 years old girl from Pakistan. She was admitted on 20.4.96 to MICU. She had fever 38.8C and generalized rash diagnosed by dermatologist as TEN due to Tegretol. The history showed that she was epiletpic since age of 5 and was controlled by Tegretol. She was free from fits for the past two years during which she had been off Tegretol. Ten days prior to admission (on 10.4.96) she took Tegretol again because her epileptic fits recurred. On 19.4.96 after 10 days of using Tegretol she got fever and generalized rash affecting face, trunk, limbs and the skin looked scalded over 90% of the body surface with affection of mouth, lips, eyes and positive Nikolsky's sign. (Fig TEN 5-1, 5-2, 5-3, 5-4). The histopathological report confirmed the diagnosis of TEN. Tegretol was discontinued and Cyclophosphamide 120 mg (3 mg/kg body weight/day) was given I.V. drip over one hour daily for seven days combined with dexamethasone 4 mg I.V. once daily for 5 days then 3mg orally daily for 3 days. On 24.4.96 she was transferred from MICU to burn unit. She had maximal improvement on the fifth day of admission and was cured after 6 more days (Fig. TEN 5-5, 5-6). She was discharged 30.4.96 on sodium valpoate.

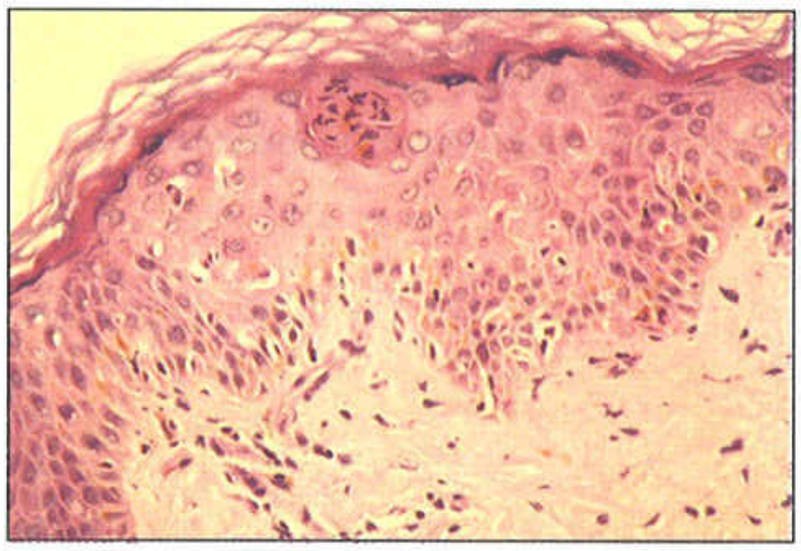

Fig. 5-3: Early necrotic changes of epidermis

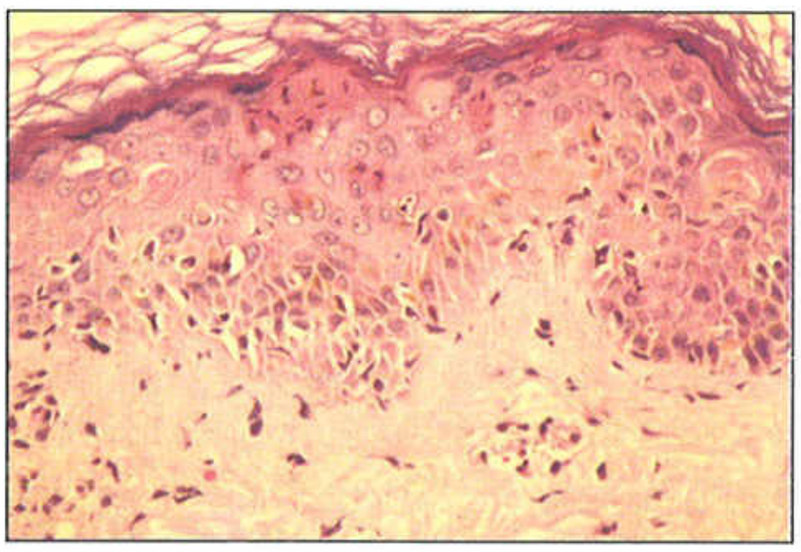

Fig. 5-4: Early necrosis of epidermis

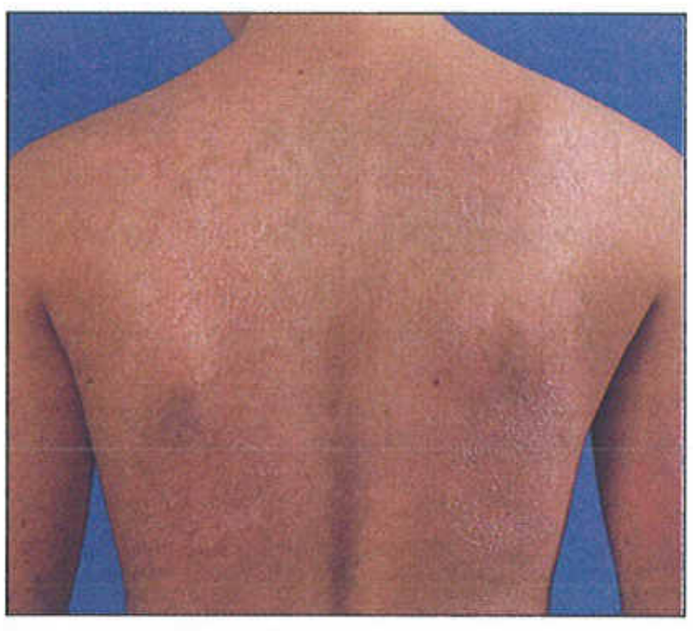

Fig. 5-5: Complete cure showing back of trunk

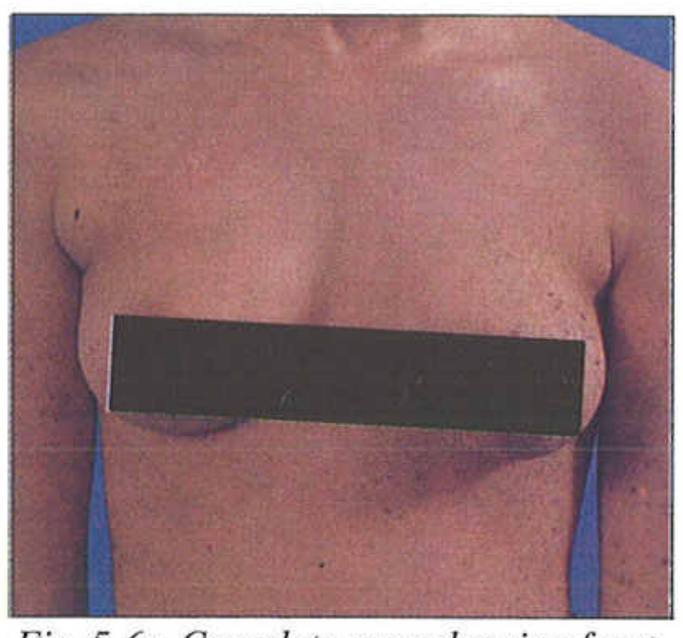

Fig. 5-6: Complete cure showing front of trunk

Discussion:

H.M.C. is the only referral center in Qatar. The five cases of TEN reported from July 1994 till April 1996 (Table 1) may represent an incidence of 5 per million per year which is relatively high when compared with 1.3 per million per year in France, Germany and Italy [2,3,4]. All Cases in Qatar were exclusively drug induced mainly anticonvulsant (60%). The most commonly reported drugs causing TEN were sulfonamides, anticonvulsants, NSAD and certain antibiotics [7]. Griseofulvin was also reported to cause TEN (33). Indomethacin is the lowest risk NSAD to cause TEN [2]. Drugs taken for more than 3 weeks would unlikely cause TEN. The time between the rash and exposure to the offending drug is between 1 and 3 weeks [7]. The determination of a single factor precepitating TEN is often difficult but an accurate history of medication taken usually helps to figure out the cause.

The incidence of TEN depends on the prescribing habits of a particular region. The free dispensing of medication in Qatar may have lead to an over exposure of the population to many drugs - a factor that may be partly responsible for the relatively high incidence of TEN in Qatar (5/million/year).

The female to male ratio in this series is 2:1 a finding similar to figures published by others[7]. Two of the reported cases were children, one adulescent and 2 adults (Table 1). The time between exposure to the drug and the appearnce of the rash in this series varied between two and twenty days. The commonest prodromal symptoms were fever, sore throat and cough. The acute phase of the eruption lasted 2-13 days with an average of 7 days. The skin in all cases had a scalded appearnce and 2 had the scalp also affected. It is reported that the scalp is usually spared[7]. All cases had affection of mucous membranes. Skin biopsy to confirm the diagnosis was done in 4 and the fifth refused both biopsy and photography. The histologic similarity between TEN and erythema multiforme is known. Immunocytochemical and electron microscopic examination (EM) could help confirm diagnoses of TEN. By the use of EM close contact between dyskeratotic keratinocytes and mononuclear cells (satellite cell necrosis) is sometimes observed in TEN[34].

The region around the basal keratinocytes show widespread lytic changes with separation of the epidermis suprabasally is frequently observed thus leaving isolated basal keratinocytes attached to the underlyhing basement membrane[11]. The histopathology of case number one showed suprabasal as well as subbasal separation (Fig TEN 1-4).

In the present series 4 of five patients were treated in the intensive care unit and or burn unit and all were cured. This result is primarily due to the high standard intensive care facilities and the efficiency of it's staff. The use of combined treatment with cyclphposphamide and systemic steroid proved life saving in these patients and the average dose of cyclophosphamide was 3-5 mg/kg body weight per day and that of dexamethasone was 0.1 - 0.12 mg/kg body weight per day. Both were given for a period that varied from 5-8 days according to severity. Several studies showed that steroids are detrimental in TEN and should be avoided[7,35]. The use of high doses of steroid (240-1000 mg. hydrocortisone equivalent) is controversial. Steroids is given to reduce both inflammation and keratinocyte necrosis but it may increase the risk of infection, delay healing, cause intestinal bleeding[30] and may be associated with progression of TEN[11].

The dose of dexamethasone we used was mainly to inhibit tumor necrosis factor alfa which is mainly produced by activated macrophages and keratinocytes may contribute to the production of widespread necrolysis after the occurance of the initial isolated necrosis of keratinocytes that were damaged by cytotoxic lymphocytes[11,36]. The cyclophosphamide beneficial effect is attributed to its inhibitory effect on cytotoxicity produced by cutaneous T lymphocytes in TEN. Biopsy specimen taken from skin after cyclophosphamide treatment of a patient with TEN revealed marked reduction of CD3+, CD8+; CD2, interleukin-2 receptor and Dr epitopes[11].

Drug related TEN is reported to have a mortality of 19%[28]. Idiopathic TEN has a mortality rate of 45%(28). The morality rate in GVHD related TEN is 100%[34]. The prognosis of TEN improves with early adequate treatment.

Table (1) 5 Cases of TEN seen in Hamad Medical Corporation from 17. 7. 94 till April 1996

Sl. No.	Pt. ini-tials	Age. Year	Sex	Disease	Drug Inducing TEN	Duration of exposure to drug before prodroma	Prodromal symptoms & its duration	Days of rashing	Mucous membrane affection	% of skin affected	Result of biopsy	Dose of I.V. cyclophosphamide given in mg/kg of body weight per day	Dose of dexame-thasome given in mg/kg of body weight per day	Result
1.	SSG	2.5	M	Febrile seizures	Phenobar-bital	4 days	Fever cough for 5 days	13 days	Eyes and mouth	95% + scalp	TEN	4.4 for 7 days	0.11 for 7 days	Cured
2.	FM Ns	6	F	Epilepsy	Lamactal	20 days	Fever for 2 days	6 days	Eyes and mouth	90% scalp	TEN	3.3 for 7 days	0.1 for 7 days	Cured
3.	J.M. S.	34	M	Epilepsy	Tegretol or Sodium Valpoate or Amoxicillin	Unknown for Tegretol and sodium valpoate one day for amoxcillin	4 days fever if anti-convulsants were the cause	12 days	Eyes and mouth	100% scalp	TEN	5 for 8 days	0.1 for 8 days	Cured
4.	NSH	33	F	Dysmenor-Rhoea	Brufen (NSAD)	2 days	Fever + sore throat + pharygeal oedema 2 days	3 days	Pharyngeal oedema	30%	Biopsy was not done	2.5 for 5 days	0.1 for one week	Cured
5.	F.B.	14	F	Epilepsy	Tegretal (Anti-convulsant)	10 days	Fever one day	2 days	Eyes and mouth	90%	TEN	3 for 7 days	0.1 for 5 days	Cured

Conclusion:

The combined use of cyclophosphamide and dexamethasone was highly effective and cured 5 patietns with severe TEN in a weeks time without any complication. The side effects of the drug were carefully monitored and the patients are best nursed either in intensive care or burn unit.

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