

stage and, although no extracutaneous sign of the disease could be demonstrated early, we suspected disease activity in the spleen, because of enlargement of this organ. Splenectomy was planned but could not be carried out because of the impossibility to find compatible blood. The histologic findings in our case were consistent already in the cutaneous phase with malignant histiocytosis (Tubbs *et al.*, 1980; Cabone *et al.*, 1981).

An early diagnosis of malignant histiocytosis is of great importance in order to start adequate therapy. In the present case we used single cell DNA measurements by flow cytometry sequentially during the course of the disease. When the disease was in the cutaneous stage, only a hyperdiploid cell clone apart from the normal cell population could be demonstrated. Contrary to this, when the disease became disseminated a large hypotetraploid cell clone could be demonstrated in skin, lymph node, but not in the blood. These findings point to a more malignant evolution during the progression of the disease and we suggest that DNA measurements upon tumours may predict the transition from the cutaneous to the disseminated stage.

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Seasonal bullous eruption due to mosquitoes

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Twenty-nine patients suffering from seasonal bullous eruption (SBE) are described and evidence is presented that the lesions were due to mosquito bites, field studies revealing *Aedes detritus* to be the causative organism. Gravitational factors are shown to play a part in the localization of the lesions to the lower legs.

Insect bite reactions are well described but, in comparison, bullous lesions, particularly of a seasonal nature, appear to be less common. The production of bullae from mosquito bites has been known for some time (White, 1871; Brown, Griffith & Erwin, 1938; Heilesen, 1949) and mosquitoes have been suspected of being the cause of seasonal bullous eruption (SBE) (Genner, 1929). Mosquitoes are known to have a seasonal activity (Holstein, 1967) which is affected by climatic conditions (Rao *et al.*, 1973) but since feeding after biting is brief and the bite is only felt in a few patients (Service, 1971) the diagnosis is usually circumstantial. The present study was undertaken to establish the cause of SBE in the Morecambe Bay area of the North of England.

Patients and methods

General practitioners in the Morecambe Bay area were asked to refer all cases of SBE over a 10-year period from 1972–1982. Twenty-nine patients were examined, of whom 27 were female and all came from a localized area within 2–3 miles from the coast where salt marshes are prevalent. A seasonal occurrence of the lesions was apparent in the summer months between June and October, August having the highest incidence (Fig. 1). The average age of the patients was 50 years (range 26 to 85).

All of the bullae occurred on or below the knee, usually bilaterally—except in one patient where it always occurred on the same leg (Figs 2, 3). Bites were observed on the rest of the body (five patients) but these took the form of minute vesicles or papules, bullae never being

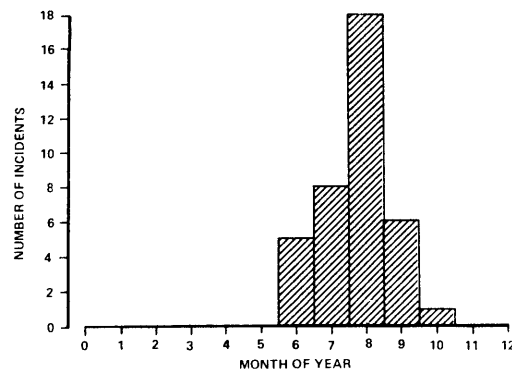


Figure 1. Monthly distribution of the number of incidents of SBE.



Figure 2. Bullae around the right knee and a healed lesion just below.

observed. The largest bulla measured 6 cm in diameter and average size was 1.6 cm. The maximum number of bullae on any one patient was 16 (mean 3.1) and 14 patients had single lesions. The bullae were all tense and circular with the exception of five which presented with an oval or irregular edge. They were filled with a clear, straw-coloured fluid. Twenty-two of the bullae had an erythematous band around the margin, in six there was surrounding oedema and in one patient this was marked involving the upper foot and lower leg. Patients observed that the



Figure 3. Tense bullae just below the knee (same patient as Fig. 2).

lesions started as tense minute vesicles which rapidly enlarged to their maximum size in the next 24 h. If undisturbed the bullae remained intact for as long as 14 days, epithelialization occurring beneath the blister, although occasionally bullae would collapse and then regrow and this was observed in three patients.

Symptoms of itch and pain were not universal, itching being only complained of in 12 patients and then only for the first 24 h. Eight patients complained of pain, the pain disappearing after a few days.

A full medical examination and history was undertaken to see if an allergic diathesis or gravitational factors predisposed to the production of SBE. One patient had atopic eczema and allergic rhinitis. Two gave a previous history of severe reactions to insect stings and 11 had previously experienced SBE. Several patients had gravitational problems on the lower legs and a comparison was made with a control group of 120 patients randomly selected and matched for age and sex. The abnormalities compared included varicose veins, superficial thrombophlebitis, deep venous thrombosis and injury to the legs (Table 1).

Table 1. Comparative analysis of patients with SBE (χ^2 analysis with Yates correction)

	n	Varicose veins (%)	Superficial thrombophlebitis (%)	Deep venous thrombosis (%)	Leg injury (%)
SBE	24	20.83	8.33	12.50	20.83
Control group	120	5.83	5.00	1.67	11.67
		$P < 0.05$	$P > 0.5$	$P < 0.05$	$P > 0.5$

Entomology

Field studies at the residences of three patients suffering from recurrent SBE revealed the only biting insect to be the mosquito *Aedes detritus*, the one exception being the mosquito *Culex pipiens* when a single specimen was found. Small ponds or water containers showed heavy concentrations of larvae and the removal of these stopped the production of further lesions in affected patients.

Aedes detritus mosquitoes were collected and allowed to starve for several days. They were then allowed to bite volunteer patients who had suffered from SBE. The mosquitoes were placed on the lower leg and on the forearm and allowed to feed until satiated in order to produce the optimum response (Rockwell & Johnson, 1952). They were then examined both macroscopically and microscopically to confirm the maximum ingestion of blood. The first patient developed erythematous papules 1 mm in diameter at both sites after 24 h. The second patient developed a similar lesion on the forearm within 24 h, but on the leg a bulla 6 mm in diameter appeared after 24 h, increased in size to 3 cm over the next 24 h and then healed over the next 14 days. The final patient developed a similar bulla on her leg which healed within 9 days but on her forearm a 2 cm white wheal developed within 1 h and then the whole of the forearm became erythematous and oedematous within 24 h.

Investigations

The fluid from 11 bullae was obtained under sterile conditions and cultured with negative findings. Microscopic examination of the fluid showed no evidence of cells present but Tzank smears taken from the base of the bullae revealed lymphocytes, neutrophils or acantholytic cells in a few patients. Excision biopsies were taken from three patients within a few hours of the onset of the lesions and histological examination showed a subepidermal bulla with the presence of a chronic inflammatory infiltrate in the upper dermis. A mild perivascular inflammatory cell infiltration was present in the superficial and deep dermis. In one instance many eosinophils were present. The histological findings were consistent with changes produced by insect bites (Rockwell & Johnson, 1952). Direct and indirect immunofluorescence was negative.

Discussion

Localized bullous pemphigoid (Pearson, Rogers & Perry, 1976) may be confused with SBE but in the latter condition single lesions are common and immunofluorescence is negative. Phytophototoxic dermatitis from plants such as Hogweed (Francis, 1970) or Meadow grass (Bellringer, 1949) may produce seasonal bullae but there may be a history of exposure to the plant and there is evidence of streaking which was absent in the present series of SBE. In North America, blister beetle dermatitis is a common cause of SBE (Lehmann, Pipkin & Pessman, 1955) but the lesions are frequently linear. Blister beetles do occur in England but no evidence was found of them in the present series and attempts to produce kissing lesions (Kerdel-Vegas & Goihman-Yahr, 1966) by the application of a piece of blister roof to normal skin was negative. Horse flies may produce bullae (Rook, 1979) but the bite is invariably painful and the fly almost always seen.

SBE has three unusual aspects. The first is its almost exclusive occurrence in females. Humans are known to have a differential attractiveness to mosquitoes (Khan *et al.*, 1969) but sexual factors have not yet been reported as playing a role. Insect opportunism determined by the difference in clothing worn by the two sexes may be the reason, but in this series four women and the two men wore trousers at the time of production of lesions suggesting that clothing may not be important.

A second feature of SBE is the absence of young people from this series. This is a group with a high exposure risk, children wear less clothing than adults and in addition their sensitivity to mosquito bites tends to be higher than adults where repeated exposure leads to the development of tolerance (Gordon & Crewe, 1948). Many patients had attacks over a number of years without the development of tolerance and one patient developed multiple lesions on six separate occasions on the same leg suggesting a local physical factor.

The third unusual factor is the localization of the lesions to the lower limbs. Mosquitoes usually feed on exposed skin, although the African mosquito *Eratmopodites theobaldi* (Haddow, 1956) has been noted as biting only 50 cm above the ground, *Aedes simpsoni* bites on the head (Haddow, 1945) and *Sabethes belisatoui* on the nose (Gillet, 1971). Other mosquitoes appear to bite selectively but the reason here is one of opportunism. *Aedes detritus* has a low flight path and therefore may arrive at the lower legs first which could account for lesions occurring at this site (Service, 1982; personal communication). However, opportunism cannot be the sole reason for the localization of lesions since bites were observed on the upper parts of the body in several patients but these were non-bullous. The experimental production of lesions could only produce bullae on the lower legs and this would suggest a specific localizing factor in the lower legs.

Vascular factors are considered to play a part in the localization of the bullae in localized pemphigoid (Pearson *et al.*, 1976) and in the present series there was a significant increase in the incidence of varicose veins and deep venous thrombosis in those patients suffering from SBE. Gravitational problems in the lower legs tend to occur in older women (Anning, 1952) and stasis dermatitis is commoner in summer due to venous engorgement (Dostrovsky & Evans Paz, 1961).

The evidence from the present series suggests that although altered immunity and insect opportunism may play a role in the localization of SBE due to the mosquito *Aedes detritus*, vascular factors play a significant role in the pathogenesis of the condition.

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Clinical use of vitamin A and its derivatives—physiological and pharmacological aspects*

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Vitamin A-therapy embraces at least three distinct fields of application. In the first application, therapy is instituted to relieve or to prevent symptoms related to vitamin A deficiency. In the second, the pharmacological effects of high (near-toxic) doses of vitamin A are employed especially in diseases characterized by excessive keratinization of the skin and mucous membranes. In the third, which is becoming increasingly common, synthetic derivatives of vitamin A (retinoids) are used topically or systemically against a number of dermatological and oncological disorders in order to influence the differentiation of epithelia and possibly also of other tissues. It should be borne in mind that, in the two latter situations, the pharmacological effects obtained, will be accompanied by the stimulation of several of the physiological functions of vitamin A. It is appropriate, therefore, to discuss the function and metabolism of vitamin A before addressing the therapeutic use of vitamin A and its derivatives which is the primary aim of this review.

Function and metabolism of vitamin A

For a full report about the biological effects of retinoids, the reader is referred to some of the comprehensive reviews appearing lately (Bollag, 1983; Pawson *et al.*, 1982; Sporn & Roberts, 1983; Zile & Cullum, 1983).

Some biological roles of vitamin A and the functional relationship between vitamin A and the synthetic retinoids are shown in Fig. 1. Retinol is oxidized, reversibly, *in vivo* to the aldehyde retinal, which is important in vision. Retinoic acid is a major oxidative metabolite of retinal. Unlike retinol, which is stored in the liver, retinoic acid is not stored and is rapidly excreted. Retinol is necessary for growth, for differentiation and maintenance of epithelial tissue, and for

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