Skin Manifestations of Immunological Origin

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Blisters are a feature of many skin reactions but the diagnosis and aetiology of chronic bullous disorders remained a problem until immunological methods threw more light on the subject.

During the last ten years it has become possible to differentiate bullous disorders that show the binding of immunoglobulins and complement to the intercellular substance in pemphigus and to the basement membrane zone in pemphigoid (Beutner and Jordan, 1964; Beutner et al., 1970). Cicatricial pemphigoid (Bean, 1974) and Herpes gestationis can also be distinguished by similar methods (Provost and Tomasi, 1973).

So reliable now are the serological results that it has been suggested (Beutner et al., 1973) that they can replace skin biopsy. At present, however, we continue to use the traditional skin biopsy as well as immunological techniques.

Two main methods of investigation are used in the chronic blistering eruption (Cormane et al., 1973): direct immunofluorescent staining of the skin taken either from the blistered area or, more often and most usefully, from apparently normal skin, and the use of fluorescent dye to demonstrate the presence of immunoglobulins and complement bound to the tissue. The level at which the immunoglobulins and complement are deposited in the skin is significant in diagnosis. In addition, the indirect method of investigation demonstrates antibodies, either to intercellular substance or to basement membrane zone, present in the sera of patients.

In order to illustrate the value of immunological methods, four patients who have recently been treated in our Department will be described. They include examples of Pemphigus vulgaris, Pemphigus foliaceus, pemphigoid and Dermatitis herpetiformis.

Whether the actual damage to the skin is by an antigen antibody reaction remains to be proved, but artificial blisters have been produced in tissue cultures grown in serum from patients suffering from pemphigus (Michel and Ko, 1977). Intra-epithelial lesions have been produced in monkey epidermis by intramucosal injection of pemphigus antibodies (Holubar et al., 1973).

Pemphigus vulgaris
This is the rarest of the diseases and the most deadly; before the coming of steroids it was invariably fatal. The disorder usually starts on the mucous
membrane and may be referred to the ENT surgeon, the dentist, or the gynaecologist. It has a high incidence in Jews. Though rare in children in this country, the most recent patient we have investigated and treated was a girl of 15.

Case History. In January 1976 a 15-year-old schoolgirl developed blisters and ulcers in her mouth. Six weeks later a blistered eruption appeared on her face and hands and she was admitted to hospital in March. Her face had the appearance of impetigo with crusted erosions, the mucous membrane of her mouth was eroded, and she also had erosions of the mucosa of the vulva and vagina. Extensive crusted lesions were present over the whole body. She was febrile and looked ill. Skin biopsy showed an intra-epidermal bulla situated just above the basal layer of cells and containing acantholytic cells in the cavity (Fig. 1). These are epidermal cells that have lost their ability to adhere to each other and are deeply staining. Direct immunofluorescence of both involved an apparently normal skin demonstrated IgG and complement present on the intercellular substance between the epidermal cells (Fig. 2). On indirect immunofluorescence, antibodies to epidermal desmosomes (intercellular material) were found in a titre of 1 in 20. These findings conclusively proved a diagnosis of Pemphigus vulgaris and treatment was started with prednisolone and azathioprine. Within four weeks her skin had healed and by September her immunological tests had returned to normal.

It is intriguing that an identical pemphigus syndrome has recently been

Fig. 1. Section of skin showing suprabasal split and acantholytic cells.
Fig. 2. Section of skin showing immunofluorescence of intercellular substance.
reported in patients on penicillamine (Hewitt et al., 1971; Tan and Rowell, 1976) and rifampicin (Gange et al., 1976). It may also accompany Hodgkin’s disease (Naysmith and Hancock, 1976).

It would seem that, like other autoimmune diseases, Pemphigus vulgaris can be precipitated by drugs and by abnormal cell products.

**Pemphigus foliaceus**

This is much more benign than Pemphigus vulgaris and is similar to an endemic disorder called Fogo selvagem that occurs in Brazil. It can be controlled in most cases with local treatment alone but our most recent patient was very severely affected and the diagnosis was not recognised early because he had no visible blistering.

*Case History.* The patient was a male fork-lift driver, aged 21, who had worked for several years in a chemical processing plant. In April 1976 he developed on his shoulders and chest an irritable eruption which was ascribed to irritation from the chemicals he handled. Gradually, despite treatment with topical steroid applications, the eruption spread to involve all his skin except the tips of his fingers and nose. He was admitted in July 1977. He looked ill and was covered with a confluent scaly and crusting eruption from the top of his scalp, over the whole of his face and trunk to his digits (Fig. 3). Only the fingers showed traces of blister formation (Fig. 4).

Skin biopsy of a finger showed a subcorneal intra-epidermal split with acantholytic cells in the cavity. Direct immunofluorescence demonstrated IgG and C3 on the intercellular material between the epidermal cells. Antibodies to intercellular material were present in his serum, a titre of 1 in 20. The clinical appearance, relatively slow progress and the investigations confirmed the diagnosis of Pemphigus foliaceus.

Treated with prednisolone 50 mg daily, azathioprine 50 mg b.d. controlled his eruption within three weeks and he was discharged on a diminishing dose of immunosuppressant drugs.

Like Pemphigus vulgaris there is a link between Pemphigus foliaceus and other autoimmune diseases such as myasthenia gravis and lupus erythematosus. In fact, in one patient with myasthenia gravis anti-epithelial antibodies were found three years before a skin eruption appeared (Peck et al., 1968).

**Pemphigoid**

This is very much a disease of the elderly, and in our ageing society the incidence is rising.

*Case History.* A widow aged 77 was admitted having developed erythematous urticarial plaques three weeks previously. She had been in good health and was taking no drugs. Intact tense blisters erupted on the urticarial areas, particularly on her limbs where the blisters became filled with blood (Fig. 5). Skin biopsy
Fig. 3. Pemphigus foliaceus to demonstrate scales without apparent blisters.
showed a sub-epidermal blister. Direct immunofluorescence demonstrated IgG and C3 on the basement membrane zone in the involved and uninvolved skin (Fig. 6). Her blood contained no antibodies to basement membrane zone, but they are present in only 70 per cent of patients (Beutner et al., 1970). She was treated
with prednisolone 40 mg and azathioprine 50 mg daily and the eruption cleared in three weeks. She is now on a maintenance dose of prednisolone 7.5 mg daily.

Why pemphigoid suddenly appears remains a mystery, but the prognosis is good, and 19 of our last 20 patients left hospital with the eruption controlled. Treatment can often be discontinued and the patient remain well for years.

Fig. 5. Pemphigoid blisters and urticarial areas.
Fig. 6. Immunofluorescence with IgG on basal membrane zone typical of pemphigoid.
Dermatitis herpetiformis

This disorder can easily be missed by being mistaken for eczema or even scabies. The discovery that virtually all patients suffer from a gluten enteropathy (Marks et al., 1966) and that the HLA type is A8, similar to coeliac disease (Seah et al., 1976) links it closely to the immunology of coeliac disease.

Doubtful cases can be diagnosed readily by the demonstration of IgA beneath the basement membrane of the epidermis of uninvolved skin (Fry and Seah, 1974). That the enteropathy is related to the eruption has recently been shown in patients who remained rigidly on a gluten-free diet, becoming free from their skin eruption without needing to take dapsone to control itching (Fry et al., 1973; Harrington and Read, 1977).

Case History. A male aged 23 working overseas developed an itching rash in December 1975, treatment with topical steroids failing to control his eruption. When he was first seen, in June 1977, he showed the classical papulo-vesicles of Dermatitis herpetiformis on his shoulders, elbows and knees. He had HLA type A8. A linear deposit of IgA was found beneath the epidermis of uninvolved skin (Fig. 7). A jejunal biopsy demonstrated partial villous atrophy. The eruption cleared within two days of taking dapsone 100 mg daily and he was advised to take a gluten-free diet.

To recapitulate the significant differences between the blistering diseases. In Pemphigus vulgaris there is splitting of the epidermis just above the basal layer and direct immunofluorescence of IgG and complement on the intercellular substance of both involved and uninvolved skin. The serum shows the presence of antibodies against intercellular substance in 90 per cent of cases and the titre reflects the severity of the disease.

In Pemphigus foliaceus the splitting of the epidermis occurs rather higher than in Pemphigus vulgaris but otherwise the findings are the same in that IgG and C3 are present in the intercellular region and serum antibodies are present, though usually in lower titre.

In pemphigoid there is a sub-epidermal bulla, which is why the blisters remain intact. There is a direct deposition on the basement membrane zone of IgG, and IgG basement membrane antibodies are present in the serum in about 70 per cent of patients but the titre does not relate to the extent of the disease, which was very apparent in the case described above.

In Dermatitis herpetiformis there is a sub-epidermal bulla with IgA present in the dermal papillae and in the unaffected skin, either in linear or granular distribution. There is a tissue type of HLA 8 in 80 per cent of cases and a gluten enteropathy in 90 per cent with anatomical and pathological changes in the jejunal mucosa.

My object has been to show how much the immunologists have assisted in the differentiation of a variety of rare yet important skin disorders. I have of necessity had to leave the impression that all is now understood. It is not. There are still
Fig. 7. Immunofluorescence of linear deposition of IgA in unaffected skin.
patients who show features of two disorders, others who show clinically typical disease but immunologically do not fit. Our knowledge is advancing rapidly and the misfits are getting fewer.

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