soaked in pure phenol by means of a chisel-shaped orange stick and leaving it there for a minute after wiping off the excess. This can be repeated at weekly intervals for two or three weeks. Every night the patient should paint round the affected nail-fold with some antiseptic in spirit or acetone so that it will penetrate into the pocket; it is obvious that an ointment is useless for this purpose, though there is a stage, as mentioned below, where it may have a place. Every dermatologist has his own favourite antiseptic application, and in my opinion the most effective is:

Mercuric chloride	1%
Brilliant green	1%
Industrial spirit	99%

The disadvantage of this substance is its vivid colour, but many patients are quite prepared to put up with this if it does them good. A less conspicuous and nearly as effective antiseptic is tincture of merthiolate, and recently I have been using the following, which is colourless and is active against candida as well as ordinary bacteria: domiphen bromide ("bradosol") (1 in 500) in 75% spirit.

While the above treatment will cure many cases there is no doubt that better results are obtained if it is assisted by a course of superficial radiotherapy. Why this works so well it is difficult to say, as the doses given, 100–150 r, have no action on the invading bacteria; I believe the effect is produced largely by diminishing the inflammatory reaction so that the nail-fold returns to its normal anatomical state and also possibly by removing obstruction to the lymph flow by inflammatory products.

A striking example of the benefit of x rays was shown in the following remarkable case.

A girl aged 6 was brought to me with a history from 6 months old of recurrent septic lesions starting at the base of the nails as a red glossy swelling which frequently oozed pus. Every nail except that of the left little finger had been involved one or more times, though not necessarily all together. She had been thoroughly overhauled elsewhere and had had a tonsillectomy two years previously without benefit. The only relevant detail in the family history was a history of eczema in the father. All simple forms of treatment had had no effect, but lesions were said invariably to clear up after x-ray treatment. When I examined her she had typical perionychia of the right index and little fingers and the left thumb. There was no evidence of any abnormality such as epidermolysis bullosa. Bacterial investigation showed a *Staphylococcus aureus* sensitive to all antibiotics except penicillin. Careful investigation for septic foci, including x-ray examination of her sinuses, was negative. Ordinary treatment, including chlortetracycline ointment, produced no improvement, but after I had found out how much radiation she had had, I gave her three fractional doses at monthly intervals, and since then she has remained clear for six months. I have no explanation for this child's extraordinary susceptibility, but she is a witness to the remarkable effect of x rays.

When the pocket at the base of the nail has been made sterile and the swelling of the nail-fold has been flattened, it is important to prevent further reinfection before the nail-fold has become firmly adherent to the nail again. This can often be helped by applying "portex" plastic skin to the base of the nail so as to seal the space between the nail and the nail-fold. It will have to be reapplied every two or three days. An alternative, though less satisfactory, method is to apply an antiseptic ointment with a water-immiscible base such as soft paraffin—for example:

Ammoniated mercury	10 gr. (0.65 g.)
Soft paraffin	to 1 oz. (31 g.)

[not the ordinary *National Formulary* ointment, because this has a water-miscible base]

This ointment should be lightly massaged into the nail-fold so as to occlude the pocket. Finally, even when the nails are back to normal the patient must continue to take reasonable precautions, otherwise there is a considerable chance of a relapse. One useful measure is to apply regularly a waterproof barrier cream round all the nails before doing any wet work.

Summary

The incidence of chronic perionychia is reported and the aetiology discussed.

Curative and preventive measures are described.

REFERENCES

- Handfield-Jones, R. M., and Porritt, A. E. (1948). *Essentials of Modern Surgery*, 3rd ed., p. 252.
Ingram, J. T., and Brain, R. T. (1955). *Sequeira's Diseases of the Skin*, 6th ed.
Ormsby, O. S., and Montgomery, H. (1948). *Diseases of the Skin*, 7th ed.

DIAGNOSIS AND TREATMENT OF PEMPHIGOID

REPORT ON 22 CASES

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Pemphigus has achieved a notoriety out of proportion to its incidence because it is one of the few fatal skin diseases. The label of pemphigus was at one time given to any chronic bullous eruption occurring in later life, but the whole conception of the disease has been altered by the observation of histological differences between the bullae formed in pemphigus and those of other blistering eruptions (Civatte, 1943). Once Civatte's histological method of diagnosis was confirmed (Rook and Whimster, 1950), it became possible to note differences between the clinical picture in pemphigus and the disease which had previously been grouped with it and which is now known as pemphigoid (Lever, 1953; Rook and Waddington, 1953; Church, 1953).

The differentiation is of more than academic importance, as the prognosis of the diseases differs. One of the most important differences is in the age groups affected; pemphigus vulgaris predominantly occurs in middle age, but pemphigoid is a disease of old age. With increasing longevity pemphigoid, like other diseases of old age, seems to be becoming more common. Recent advances in treatment of the disease with corticotrophin (A.C.T.H.) and cortisone have improved the prospects of recovery, but early recognition and treatment are important, since many patients become bedridden and die as the result of this rather than of their skin eruption.

Clinical Features

We describe below the clinical features of pemphigoid as they have been observed by us in 22 cases. We believe that in the great majority of cases a diagnosis of pemphigoid can be made on clinical grounds alone, and this can be confirmed histologically.

Most patients with pemphigoid are over 70; the oldest we have encountered was aged 89. They may be in good health at the time of onset, but a significant number, even when age is taken into consideration, suffer from some chronic illness which causes them to be bedridden. Malignant disease has been said to be an associated illness, but did not occur in our series of cases.

Pemphigoid commonly starts with a non-specific rash on the limbs that may be urticarial or, occasionally, eczematous.

When urticarial this stage lasts one to three weeks before bulla formation occurs, but when eczematous the blisters may not appear for two to three months. As Rook and Waddington (1953) have pointed out, some cases start with a localized group of blisters, which may persist for several weeks and present a diagnostic problem to those unfamiliar with the subsequent course of the disease. These "primary lesions" often occur at the site of some existing skin injury such as a gravitational ulcer. We have also seen the first blisters on the scar of a cicatricial alopecia, on the scar of burns, and, more than once, around the umbilicus. If the patient is fortunate and survives the generalization of the rash, the primary area often continues to blister when the rest of the skin has healed.

Sudden generalization of the true eruption of pemphigoid follows these prodromal eruptions and most of the body is affected within a week. Severe irritation may precede the eruption. At first areas of dusky raised erythema appear, bearing an ominous resemblance in tint to post-mortem

Characteristic pemphigoid eruption showing discoid erythematous plaques with superimposed blisters. (Case 8.)

livido. Blisters soon follow on both erythematous and apparently normal skin and sometimes form a gyrate pattern at the edges of the zones of erythema (see Illustration). The blisters are tense and dome-shaped, and vary in size from vesicles to large bullae 2-3 in. (5-7 cm.) across. Their contents are usually clear serum, but occasionally are blood-stained. Though large, the blisters are remarkably tough and may remain intact for several days, and occasionally the serum coagulates. In some blisters the serum is absorbed, so that the epidermis settles back in place like a skin graft, but the majority rupture and form erosions which crust and heal with remarkable speed, leaving a pigmented stain.

Mucosal lesions consisting of blisters and discrete erosions are usually confined to the oral mucosa, which is affected in more than half the cases, but usually after the generalized eruption has appeared. The mouth lesions are rarely severe, and, like the erosions on the skin, heal fairly readily. The illness is usually accompanied by a leucocytosis with a variable increase in the eosinophil count, which is of little diagnostic significance. A fever is unusual, but this may be due to the tendency for the aged to remain apyrexial in what would be a febrile illness in a younger subject.

The eruption of blisters and erythematous areas is cyclical and the interval between fresh crops of blisters varies from a few days to two or three weeks. The periods of quiescence may therefore raise false hopes of therapeutic success.

The course of the disease is very variable: some cases undergo spontaneous remission, while others seem to remit as a result of treatment. A fatal termination is not uncommon, the cause of death usually being bronchopneumonia. A complication which predisposes to this is generalized oedema, a result of loss of plasma proteins

through the eroded skin. Confirmation of the diagnosis of pemphigoid can be obtained by biopsy of one of the early small blisters.

The bulla of pemphigoid is subepidermal, the entire epidermis being torn off the papillary bodies and lifted into a dome by the outpouring of serum which accumulates in the cavity. The bulla is always rounded or pear-shaped, and under tension the surrounding cells are flattened into lamellae but retain a living structure with intact prickles; the lateral walls are concave and solid and do not permit fissuring. Usually the cavity is single, though there may be an appearance of loculation due to fibrous tracts or fusion with neighbouring bullae. The wrenching off of the epidermis breaks sweat ducts, tears off the tip of interpapillary buds, leaving them implanted between papillae, and stretches the collar of hair follicles. In large bullae the raised epidermis becomes thinned and sometimes necrotic. The floor of the bulla is formed by oedematous papillary bodies, and the extent of the infiltrate varies but is proportional to that in the bulla fluid and the subadjacent dermis. The number of eosinophils varies in proportion to those in the circulating blood (Civatte, 1936, 1943; Lapière *et al.*, 1946).

Differential Diagnosis

Pemphigus Vulgaris

This disease is rare compared with pemphigoid. It usually attacks those in middle age and in previously good health, though it may occasionally be seen in the later decades of life. The onset is insidious, and the first lesions usually affect the buccal mucosa; here the blisters break so rapidly that it is unusual to see intact lesions, and the patient presents with painful superficial erosions which resist treatment and may persist for many months or even a year before the disease reveals itself further. The essential lesions of pemphigus are the bullae arising from apparently normal skin and unaccompanied by the erythematous areas which occur in pemphigoid. Unlike the blisters in pemphigoid, the pemphigus lesions are small and flaccid, and rupture rapidly, so that even when the skin is extensively involved it may not be possible to find any intact blisters at any particular time. The erosions resulting from rupture of the bullae remain indolent, or extend by undermining the peripheral skin, so that large areas of the trunk become denuded of skin. The resultant clinical picture is in distinct contrast to the pemphigoid sufferer, whose erosions heal rapidly and who may be covered with large intact blisters. However, there are a few cases in which it is difficult to differentiate on clinical signs alone, and in these the histology of the bulla provides the diagnosis.

Histology.—The bulla in pemphigus vulgaris is formed by the hollowing out of a cavity in the thickness of the prickle-cell layer of the epidermis after a split has been formed by degeneration of the prickle cells. This degeneration is called acantholysis and is the elementary lesion of pemphigus (Civatte, 1936, 1943); essentially, the process consists of degeneration, ballooning, and ultimate fragmentation of the nucleus and loss of prickles and intercellular protoplasmic filaments, so that the affected cells become spherical and detached. The site of the bulla in the epidermis varies; it usually arises about the middle layer, but it may arise deep down immediately above the basal layer. The basal layer remains adherent to the papillary bodies and forms the base of the cavity. The cavity terminates at an acute angle, sometimes in a fissure with ill-defined lateral borders; and the adjacent cells, not being under pressure, remain rounded. The cellular infiltrate in the bulla varies from a few lymphocytes and histiocytes to a dense polymorphonuclear leucocytic infiltrate with a variable proportion of eosinophils. A few detached acantholytic cells are found in all pemphigus bullae. The dermal infiltrate varies and is similar in degree to that in the bulla.

The infallibility of the histological differentiation between pemphigus and pemphigoid has not been accepted by all

dermatologists. Hellier (1954) has reported one case of pemphigus vulgaris in which subepidermal bullae and intra-epidermal bullae with acantholysis were found in different phases of the disease; while Prakken and Woerdeman (1955) found both types of bullae present simultaneously in two cases. Many of our patients had more than one biopsy performed, and in all the cases of pemphigus and pemphigoid which we have treated the histology has been true to type.

Other Eruptions

Dermatitis herpetiformis and erythema multiforme may need to be considered in the diagnosis. Dermatitis herpetiformis is uncommon in old age and can be excluded by its specific response to sulphapyridine or diaminodiphenyl sulphone therapy. Erythema multiforme is an acute eruption which resolves in less than two weeks, and, although the eruption of bullae and erythema may resemble pemphigoid, its duration is diagnostic.

Present Study

The accompanying Table shows the main features of the 22 cases of our series. It will be seen that the sexes are affected equally. The age range was from 59 to 89, the average being 76. In half the cases the oral mucosa was involved, but this occurred in several of the cases which recovered and was not necessarily a bad prognostic feature.

One histological finding in this series was invariably a subepidermal bulla with no evidence of acantholysis. The site of origin of the disease was more often on the limbs than on the trunk.

Mode of Onset

We describe below two short histories of cases which appear in the table to illustrate the variable mode of onset.

Case 4.—A retired schoolmaster aged 79 complained of an itching eruption on the arms and legs of three weeks' duration. The itching was so intense that he was unable to sleep. On examination an eczematous eruption was found on the forearms and legs, and he was treated with local applications of a tar ointment. The itching decreased and the eczematous eruption subsided for two months. Then quite suddenly dusky figurate areas of raised erythema appeared on the trunk and limbs. Tense discrete bullae erupted on the erythematous areas, and within a week he was covered with bullae up to 3 cm. in diameter.

Case 5.—A man aged 65 accidentally spilt hydrofluoric acid on his left leg. He cleaned the acid off immediately with water, but a superficial burn developed. Several days later he developed an irritating rash around the burnt area, and two to three weeks later blisters appeared on the right leg and the arms. This eruption, which was first diagnosed

as dermatitis herpetiformis, was not improved by sulphapyridine and Fowler's solution, and he was admitted to hospital two months after the onset of the eruption. On examination there was a confluent area of scaly erythema on the left leg with superficial ulceration around the ankle. Numerous haemorrhagic bullae varying in size from 1 to 3 cm. were present on the right foot and leg, the thighs, and forearms. Healing erosions and pigmented stains of healed bullae could be seen. The histological picture was of a subepidermal bulla.

Treatment

It is difficult to assess the results of treatment of a disease such as pemphigoid, which undergoes spontaneous remissions, and it is still more difficult because those over the age of 70 are affected. Any disease severe enough to warrant a lengthy stay in bed at that age will produce casualties from stasis pneumonia and thrombophlebitis.

Before the era of the corticosteroids, patients with pemphigoid did recover: in our own series, 4 out of 11 had a satisfactory remission. Various drugs were used, but none of the early treatments proved reliable.

Suramin ("antypol") has been used for many years in the treatment of pemphigus, including pemphigoid, and most dermatologists have seen cases recover after its use. It appeared to benefit three of the four cases which recovered, but it is unreliable, and is, moreover, a toxic preparation.

Chlortetracycline controls the blistering in some cases of pemphigoid—this is shown when cessation of its use is followed by a severe exacerbation—but it is not effective in all cases, and many patients cannot tolerate the high dosage necessary to control the blisters. Other forms of treatment such as sulphapyridine and liquor arsenicalis have been completely ineffective in our hands, though Rook and Waddington thought that liquor arsenicalis was of value.

The discovery that cortisone and corticosteroids were capable of suppressing blister formation in pemphigus and pemphigoid was a step forward, and the prognosis of pemphigus has improved immensely with their use. We have now treated 11 cases of pemphigoid with either corticotrophin or cortisone, and, despite the average age of 77.7, seven are alive and well, though all but one are receiving a maintenance dose of corticotrophin or cortisone.

This contrasts with 4 survivals from 11 cases, average age 74.5, treated before corticotrophin became available. The natural history of the disease is so variable and our figures are so small that the apparent improvement in mortality figures is well within the bounds of chance. There are, however, considerable advantages in the treatment with steroids. The formation of new blisters is suppressed quickly and in

Summary of Cases

Case No.	Sex	Age	Original Site	Mouth Involved	Histology	Treatment	Present State	Duration of Follow-up (Months)	Cause of Death. Found at Necropsy
1	M	79	Forearm	No	Not done	Corticotrophin and cortisone	Well	12	
2	F	75	Scalp	Yes	Subepidermal blister	"	"	18	
3	F	73	Ears and legs	No	" "	Corticotrophin	"	24	
4	M	79	Arms and legs	"	" "	"	Dead		Hypostatic pneumonia
5	M	65	Left leg	Yes	" "	"	"		Bronchopneumonia. Cirrhosis of liver
6	M	75	Umbilicus	No	" "	"	Well	18	
7	M	84	Legs	"	Not done	"	Dead		Pulmonary embolism
8	F	70	Scalp	Yes	Subepidermal blister	Corticotrophin and cortisone	"		Superior mesenteric artery thrombosis
9	M	86	Legs	No	" "	Corticotrophin	Well	12	
10	M	86	"	"	" "	"	"	3	
11	F	80	Arms	"	Not done	"	"	6	
12	M	78	Back	Yes	Subepidermal blister	Sulphapyridine and penicillin	Dead		Bronchopneumonia
13	F	79	Vulva	"	" "	Suramin	"		Lobar pneumonia
14	M	59	Feet	"	" "	Chlortetracycline and suramin	Well	9	
15	F	69	Wrists	"	" "	Chlortetracycline	"	10	
16	F	79	Forearms	No	" "	"	Dead		Cause unknown
17	F	76	Left arm	Yes	" "	Chloramphenicol	"		Senility (necropsy not done)
18	M	89	Feet	"	" "	Chlortetracycline	"		Bronchopneumonia. Cirrhosis of liver
19	F	78	Ankles	No	" "	Penicillin	"		Bacterial endocarditis pyaemia
20	M	87	Forearms	"	" "	Suramin	Well	24	
21	F	59	Back	Yes	" "	"	"	8	
22	F	67	Breasts	No	" "	Chlortetracycline	Dead		Cerebral thrombosis. Necropsy not done

most cases improvement is maintained easily and the patient rapidly becomes ambulant. This eases the nursing problem and minimizes the risk of intercurrent disease. It also shortens the duration of stay in hospital, an important consideration in these days of long waiting-lists.

The dosage required to control the blister formation in the cases which have recovered has been remarkably small, the maintenance dose being as low as 20 mg. of corticotrophin gel on alternate days. Any reduction below this amount or increase of time between doses has led to a relapse, and we have been able to stop treatment in only one of the seven surviving cases. This very small dosage is strikingly different from the amounts necessary to control the blistering of pemphigus, though it must be admitted that in one fatal case blistering continued despite a daily dosage of 400 mg. of cortisone. It is our practice to start treatment with intramuscular corticotrophin gel 50 mg. on the first day and then 20 mg. twice daily. On this dosage in all but two cases, new blisters ceased and the dose could be reduced within a few days to 20 mg. daily and the patient discharged from hospital on a maintenance dose of 20 mg. on alternate days.

One feature which we have noted on several occasions is that if the dose is lowered too much and new blisters appear again, a high dose of corticotrophin may be necessary to control the disease once more. Incidentally a relapse may be forecast by premonitory plaques of erythema.

An antibiotic—usually chlortetracycline, as it may help also to control the blisters—is given to prevent the possibility of a lung and skin infection whilst the high dose of corticotrophin is being given, but the antibiotic can be stopped when the corticotrophin dose is lowered to 20 mg. daily or less, and we have seen no serious intercurrent infection in the patients who have been living their normal lives at home on maintenance therapy. While the larger doses of corticotrophin were necessary, a low-salt diet and added potassium (1 g. three times a day) were given to prevent electrolyte imbalance, but these were stopped when the low maintenance dose was reached.

Where possible, the patient has been taught to give his own injections before discharge home, but in some of the very old patients it has been necessary to train a relative, or request the help of the district nurse.

Case Histories Showing the Effect of Corticotrophin

Case 6.—A man aged 75 was admitted to hospital with a widespread pemphigoid eruption of three weeks' duration. There was no response to chlortetracycline and suramin. Corticotrophin gel, 20 mg. daily, was sufficient to control the eruption, and the maintenance dose was 20 mg. on alternate days. He had no blisters for one year.

Case 9.—A man aged 86 was admitted to hospital in September, 1952, with a generalized pemphigoid eruption of one month's duration and a large gravitational ulcer which had been present for 30 years. He was treated with soluble corticotrophin rather irregularly owing to shortage of supplies, and after nine weeks he was discharged home apparently in a remission. It was noticeable that when corticotrophin was stopped for three or four days on several occasions the blisters recurred, but ultimately cessation of corticotrophin was not followed by a relapse. He remained well until June, 1954, when he was readmitted with a generalized pemphigoid eruption. The eruption again responded to soluble corticotrophin, and he was discharged home after eight weeks to have a maintenance dose of 15 mg. of soluble corticotrophin daily. He ceased to attend the follow-up clinic in October, and then ran out of corticotrophin. He was readmitted to hospital in December, with extensive bullae over the legs, back, and trunk. Within a month the condition was once more controlled with corticotrophin, though on this occasion corticotrophin gel in a dose of 30 mg. daily was necessary. He was discharged on a maintenance dose of 20 mg. of corticotrophin gel daily and he has so far remained free of blisters.

Case 9 illustrates the relative ease with which the condition can be controlled with quite low doses of corticotrophin, but shows that failure to maintain the treatment was followed by relapse.

Failures

One man aged 84 died three days after admission to hospital of pulmonary embolism and after only three days on corticotrophin. He had been bedridden for some weeks at home, and one could ascribe his death to embolism from thrombophlebitis of the veins of the legs or pelvis. We were disturbed, however, by the death of another patient, a woman of 70 whose eruption had not been controlled by corticotrophin or cortisone, which was substituted after a low ketogenic steroid output had suggested inadequate suprarenal response. She also died of an acute superior mesenteric thrombosis.

One might ascribe both these deaths to natural events unrelated to treatment, but we have also had two other patients with different skin diseases on corticosteroids who have died of pulmonary emboli, and we feel that there may be an increased risk of this complication in elderly patients on long-continued and high dosage of corticosteroids. This risk has already been pointed out by Cosgriff (1951).

The other two fatalities were due to bronchopneumonia, unrelated, so far as we could determine, to the treatment with corticosteroids.

Only 2 of our 11 steroid-treated cases did not respond to treatment. One continued to develop blisters despite a daily dosage of 75 mg. of soluble corticotrophin and died of bronchopneumonia; the other was the woman who died of superior mesenteric thrombosis, but whose eruption was not controlled with 400 mg. of cortisone daily.

Despite the disadvantages, it is our opinion that treatment with corticotrophin and cortisone is the method of choice in pemphigoid and should be instituted as soon as possible after the onset of the disease.

Summary

The clinical features of pemphigoid based on a study of 22 cases are described and the differential diagnosis is discussed.

The results of treatment of 11 cases with corticotrophin (A.C.T.H.) and cortisone are reported, and are contrasted with the treatment of 11 cases before the steroids became available.

Seven of the 11 cases treated with corticotrophin and cortisone survive, though all but one require maintenance therapy. Despite the advantages of this form of treatment, an increased risk of death due to thrombophlebitis and embolism is a possibility, and the disease itself was not controlled in two cases.

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ADDENDUM.—Since this article was submitted three further cases of pemphigoid, in persons aged 65, 67, and 83, have been controlled successfully by cortisone alone. The maintenance dose in these cases ranges from 100 to 175 mg. daily.

REFERENCES

- Church, R. E. (1953). *The Natural History of Pemphigus*. M.D. Thesis, University of Cambridge.
- Civate, A. (1936). In *Nouvelle Pratique Dermatologique*, by J. Darier et al., 7, 686.
- (1943). *Ann. Derm. Syph. (Paris)*, 3, 1.
- Cosgriff, S. W. (1951). *J. Amer. med. Ass.*, 147, 924.
- Hellier, F. F. (1954). *Brit. J. Derm.*, 66, 49.
- Lapière, S., van Runckelen, and Dussart (1946). *Arch. belges Derm. Syph.*, 2, 81.
- Lever, W. F. (1953). *Medicine (Baltimore)*, 32, 1.
- Prakken, J. R., and Woerdeman, M. J. (1955). *Brit. J. Derm.*, 67, 92.
- Rook, A. J., and Waddington, E. (1953). *Ibid.*, 65, 425.
- and Whimster, I. W. (1950). *Ibid.*, 62, 443.