cloudy swelling of the tubules of the kidney; this change was not so marked, however, as with corresponding doses of salicylate.

Absorption and Excretion.—The absorption and excretion of this substance are rapid; after a subcutaneous 10-mg. dose in the rat the substance appears in the urine in one hour and is nearly all eliminated three hours after injection. After administration by mouth the quantity in the urine is smaller than after a similar dose given subcutaneously, indicating that the absorption is not so complete by the oral route.

Reduction of Formalin-induced Swellings.—If 4% formalin is injected into the pad of the foot of a mouse a swelling of the lower part of the leg results which is maximal at the end of seven days. If the animal is treated with A.C.T.H., 1 mg. equivalents twice daily, from the time of the injection this swelling is considerably reduced. Treatment with γ -resorcyrate, 5 mg. daily in the diet or 0.5 mg. daily by subcutaneous injection, produced a reduction of swelling of the same order as that found with the A.C.T.H. Similar doses of sodium salicylate do not produce an appreciable effect.

APPENDIX

BY

B. E. CLAYTON,* Ph.D., M.B.

AND

F. T. G. PRUNTY, M.D., F.R.C.P.

Through the courtesy of Dr. J. Reid a sample of sodium γ -resorcyrate was received.

It has been shown that A.C.T.H. causes a depletion of the adrenal ascorbic acid of hypophysectomized rats, and the test is regarded as highly specific (Sayers, Sayers, and Woodbury, 1948). We used a group of four hypophysectomized rats and an intravenous dose of γ -resorcyrate in saline as high as 2.5 mg. per 100 g. rat, but no adrenocorticotrophic

activity could be detected. Though unlikely, this does not rule out the possibility of γ -resorcyrate acting on the pituitary gland of the intact animal. Owing to difficulties in obtaining the large number of rats required to test this, the experiment was not performed.

We described a method for consistently producing granulation tissue on the anterior abdominal wall of mice, and showed that its formation could be completely inhibited by A.C.T.H. (Clayton and Prunty, 1951). A similar effect was obtained with cortisone acetate, the dosage necessary varying with the mode of administration. Apparently γ -resorcyrate under the right conditions has similar properties.

The experimental details are summarized in the Table at the foot of the preceding column.

In addition Professor Buttle has found that equivalent doses of salicylate had no effect on healing.

Thus γ -resorcyrate resembles cortisone in its effect on healing. The dosages required are not very dissimilar. This may be deceiving, as γ -resorcyrate is so very rapidly absorbed and excreted compared with cortisone acetate suspensions.

REFERENCES

- Clayton, B. E., and Prunty, F. T. G. (1951). *Analyst*. In press.
Sayers, M. A., Sayers, G., and Woodbury, L. A. (1948). *Endocrinology*, **42**, 379.

TREATMENT OF SOME BULLOUS ERUPTIONS WITH AUREOMYCIN AND CHLORAMPHENICOL

BY

F. RAY BETTLEY, M.D., F.R.C.P.

Physician for Diseases of the Skin, the Middlesex Hospital

AND

E. A. FAIRBURN, M.D., M.R.C.P.

Senior Registrar, the Middlesex Hospital

Following the preliminary report of the treatment of pemphigus vulgaris with "aureomycin" (Bettley, 1950) we are now in a position to record some further experience with aureomycin and chloramphenicol in pemphigus vulgaris and certain other bullous eruptions.

The results obtained by others with similar treatment of comparable cases have shown a surprisingly variable response to this form of chemotherapy. Brainerd *et al.* (1949) treated three cases of pemphigus—one underwent a temporary remission, one was improving spontaneously at the time of treatment, while the third proved unresponsive. Spink and Yow (1949) observed no amelioration in two cases of pemphigus. Beinhauer (1950) treated seven cases of pemphigus vulgaris, all showing a uniform failure to improve. Philip (1950) recorded 19 cases: two passed into a long-standing remission, in seven there was transient improvement only, while in 10 there was no response. Combes and Canizares (1950) likewise reported only temporary remission or complete unresponsiveness in 12 patients. Barber and Yorke (1950) noted a short-lived remission in a case of pemphigus vegetans. Mathieu (1950) obtained a more favourable response, a case of pemphigus vulgaris being checked and being subsequently maintained in remission by maintenance therapy. This consisted of 2 g. of aureomycin daily, a smaller dosage being followed by relapse.

Likewise, diverse responses have been observed in the treatment of dermatitis herpetiformis. Robinson *et al.* (1949), Tzanck and Meyer (1949), Graciansky and Hardouin (1949), and Degos *et al.* (1949) recorded

Dose	Mode of Administration	No. of Mice	No. of Ulcers		
			Inhibited	Impaired	Healing
Cortisone acetate					
4 mg.	Merck's suspension subcutaneously two hours before making ulcer	11	11	0	0
4 "	Merck's suspension subcutaneously, divided into two injections, six hours before and one hour after cutting	3	3	0	0
2 "	Merck's suspension subcutaneously six hours before cutting	3	0	3	0
2 "	Merck's suspension subcutaneously 17 hours before cutting	2	0	2	0
2 "	Suspended in propylene glycol and saline, as two intraperitoneal injections, two hours before and one hour after cutting	2	2	0	0
1 "	" " "	2	0	0	2
Sodium γ-resorcyrate					
2 mg.	Solid implanted six hours before cutting	2	0	0	2
4 "	" " "	2	0	2	0
6 "	" " "	2	1	0	1
4 "	Suspended in arachis oil, and given subcutaneously six hours before cutting	2	2	0	0
3 "	Aqueous solution given as a series of repeated subcutaneous injections	2	2	0	0
1.5 "	" " "	2	0	2	0
3 "	Aqueous solution as two subcutaneous injections, two hours before and one hour after cutting	2	0	0	2
3 "	In propylene glycol and saline, as two subcutaneous injections, two hours before and one hour after cutting	2	0	0	2

Controls: With each experiment, controls were cut, and received cortisone diluting fluid, arachis oil, or propylene glycol and saline as necessary.

*Holden Research Fellow at St. Thomas's Hospital.

favourable responses. Robinson (1950) found intra-venous aureomycin therapy necessary in some instances if remission was to be achieved. Beinhauer (1950) treated five cases—two improved and three showed no change. Shaw (1950) was unable to demonstrate any improvement with this therapy.

Case 1. Pemphigus Vulgaris

This case was recorded in the preliminary report (Bettley, 1950).

The patient was a middle-aged Jewess whose illness started in July, 1949, with the appearance of sores inside the mouth, followed a month later by blisters and sores on the trunk. She was first seen on September 5, 1949, when she had many superficial erosions on the mucous membrane of the cheeks, gums, and lips, together with a few blisters on the trunk. During the next two weeks her condition deteriorated, and on September 20 she was admitted to hospital. By that time the typical clinical picture of pemphigus vulgaris was well developed and blisters covered a large portion of the body surface.

Procaine penicillin, 450,000 units twice daily for a week, was given without effect on the eruption of blisters. Suramin, 1 g. every other day, was given for a week, also without effect. The temperature at this time was around 100–102° F. (37.8–38.9° C.).

The patient's condition deteriorated rapidly and she ate very little because of the painful state of her mouth. At that time her condition was grave; she had lost the desire to live and, indeed, seemed certain to die. From October 13 to November 25 aureomycin, 2 g. daily, was given. Within twenty-four hours of starting this treatment her general condition improved greatly. The temperature reached normal on the third day and no fresh blisters appeared after aureomycin was started. She was discharged from hospital on December 6 with the skin completely healed.

A year later she was still quite well and had had no recurrence of the pemphigus

Case 2. Pemphigus Vulgaris

A Jewess aged 47 complained of an eruption of blisters on the skin since about October, 1949. On admission to hospital on April 18, 1950, she presented an eruption of typical pemphigus vulgaris with extensive buccal ulceration. Biopsy of the skin showed acantholysis with intra-dermal bulla formation. Tzanck's test showed pemphigus cells.

From April 19 to May 1 chloramphenicol, 2 g. daily (loading dose 4 g.), was given without apparent effect. From May 2 to 18 aureomycin, 2 g. daily (loading dose 4 g.), was given. During this period there was considerable improvement; the appearance of fresh bullae was very much reduced, while buccal lesions remained unaffected. The drug caused considerable nausea, and treatment had to be interrupted; within a few days of this the eruption of bullae again increased. From May 26 to June 29 she again received aureomycin, 2 g. daily (loading dose 4 g.). The eruption was controlled, though not completely abolished. She relapsed within a few days when treatment was stopped, again because of nausea and vomiting. From July 10 to 22 aureomycin, 4 g. daily, was given. This higher dosage was administered in an attempt at complete control of the eruption instead of the partial improvement that had been obtained before. Nausea and vomiting were a serious complication, and it is doubtful what dosage of aureomycin was really absorbed. The eruption was still largely though not completely controlled, but the patient's general condition gradually deteriorated and she died on July 22. Post-mortem examination was refused.

Case 3. Pemphigus Vulgaris

This patient was an Egyptian man aged 46. In August, 1948, he had ulcers on the mucous membrane of the cheeks and tongue, followed by conjunctivitis. Blisters developed on

the skin of the abdomen and axillae in January, 1949. After this his condition fluctuated but never returned to normal. In January, 1950, he was given 12 g. of aureomycin over a period of three days; there was considerable improvement, but the treatment was not continued. He was later given stovarsol over a period of some weeks; this gave rise to albuminuria and renal damage, which persisted. During his journey to England in September, 1950, the condition of his skin deteriorated, and when first seen on September 18 the whole surface of the body was covered with large numbers of bullae of various sizes. He was admitted to hospital the next day. The clinical appearances were those of pemphigus vulgaris. Biopsy showed intra-epidermal bullae with acantholysis. The total white blood count was 15,100, eosinophils 16%; E.S.R. 32. Fluid from a bulla contained 55% eosinophils. The patient's general condition was good and the temperature normal.

Aureomycin, 2 g. daily, was started on September 19 (loading dose 4 g.). There was at once an improvement in the condition of the skin, and the eruption of fresh bullae was almost halted. Occasional small blisters up to 0.5 cm. in diameter continued to appear, principally on the hands and feet. In the course of a fortnight's treatment all the lesions had healed with the exception of those on the hands, feet, and tongue. This state of affairs continued until October 23, when the dose of aureomycin was increased to 3 g. daily. On October 30 it was increased to 4 g. daily. Under this increased dosage the eruption of fresh lesions on the hands gradually came to an end. He was discharged from hospital on November 14 on a maintenance dosage of 1 g. daily. He later wrote to say that the condition of the hands relapsed, with the appearance of fresh blisters, on November 22; the dose was then increased to 4 g. daily, and the eruption disappeared in a few days. A further exacerbation occurred on December 17 and again responded within twenty-four hours to an increase in dosage to 4 g. daily.

Case 4. Pemphigus Vegetans

A man aged 56 first developed raw areas in the axillae and a sore tongue in August, 1947. After this the scalp and groins were affected. When first seen, on January 23, 1948, he showed multiple condyloma-like lesions on the inner surface of the thighs and on the scrotum. Similar lesions were present in the axillae. There was an irregular ulceration of the lower lip. The clinical appearances were those of pemphigus vegetans, and this diagnosis was confirmed by a biopsy carried out later.

The condition gradually resolved during the summer of 1948 and he was clear until October, 1949. The condition then gradually relapsed in the groins and axillae, and on February 19, 1950, he was admitted to hospital. He then showed an extensive eruption of pemphigus vegetans in the groins and axillae. A blood count showed 10,700 white cells, with 30% eosinophils; sedimentation rate 28 (Wintrobe). The temperature fluctuated between 99 and 102° F. (37.2 and 38.9° C.).

Chloramphenicol, 2 g. daily, was started on February 22 (loading dose 4 g.). The temperature came down in step-ladder fashion and was normal after February 27. The vegetations became progressively flatter and no fresh lesions appeared. The mouth ulceration healed in a few days. By the end of March all the lesions had completely disappeared, leaving the skin of normal texture but deeply pigmented over the affected areas.

In September the patient wrote to say that his skin had remained completely well.

Case 5. Pemphigus Vegetans

An Englishman aged 69 first had a pustular eruption in December, 1949; this was followed by the raised granulomatous lesions of pemphigus vegetans. On admission to hospital on May 10, 1950, he had extensive vegetating erosions on the forehead and around the mouth and chin. The affected areas were studded with small deep pustules

which were sterile on culture. Tzanck's test showed pemphigus cells.

Aureomycin, 2 g. daily (loading dose 4 g.), was given from May 11 to June 15. During this period the lesions seemed to epithelize, but they continued to extend and pustules continued to appear. From June 16 to July 5 he was given chloramphenicol, 2 g. daily (loading dose 4 g.), but no great change appeared. From July 6 to August 11 chloramphenicol was increased to 4 g. daily. Soon after beginning the higher dosage pustules ceased to appear and the lesions flattened. Eventually they disappeared completely, leaving behind normal skin with no scarring. During this period, on July 21, he developed signs of paraplegia with urinary retention, thought to be the result of a cerebral vascular lesion.

By about August 25 lesions of pemphigus vegetans had recurred on the forehead, mouth, axillae, anterior abdominal wall, perineum, fingers, and toes. Chloramphenicol, 2 g. daily (loading dose 4 g.), was given from September 18 to 24, but there was no improvement. From September 25 to December 4 he received chloramphenicol, 4 g. daily. As before, there was a satisfactory response to this higher dosage and the eruption eventually cleared completely. After December 4 the dosage of chloramphenicol was slowly reduced without recurrence. On January 16, 1951, chloramphenicol was stopped and the patient left hospital.

Case 6. Pemphigus Erythematosus

A Jewess aged 44 had had Seneur-Usher syndrome since July, 1948. On admission to hospital on May 18, 1950, she showed an eruption of bullae, which progressed to form oval scaly and crusted areas towards the midline of the back and front of the trunk, and the scalp. Tzanck's test showed pemphigus cells. Biopsy showed acantholysis and intra-epidermal bulla formation.

Aureomycin, 2 g. daily (loading dose 4 g.), was given from May 19 to June 16. All lesions gradually healed and she was discharged from hospital on June 27.

She slowly relapsed after an interval of about six weeks and was readmitted to hospital on December 27. From December 28 to January 18 chloramphenicol, 2 g. daily (loading dose 4 g.), was given. Again the eruption cleared up, and she was discharged free of lesions on January 26.

Case 7. Dermatitis Herpetiformis

An Englishman aged 70 had an erythematous eruption, with later the production of bullae, on the trunk and limbs, which started about December, 1949. Blisters became very much worse in March, 1950. On admission to hospital on April 12 there was a generalized eruption of blisters of all sizes, some arising on normal skin; erythematous patches were also present. No lesions were present in the mouth. Tzanck's test showed no pemphigus cells. A biopsy showed subepidermal vesicles with no acantholysis.

Chloramphenicol, 2 g. daily (loading dose 4 g.), was given from April 15 to May 1 and considerably improved the condition, but a few fresh bullae continued to appear. From May 2 to June 1 aureomycin, 2 g. daily (loading dose 4 g.), was given and improvement continued, but occasional bullae were still seen. Within three days of stopping aureomycin a very marked relapse followed, with the production of numerous bullae. Blisters were again controlled and almost entirely abolished with aureomycin, 2 g. daily, from June 13 to 29; then until July 17 aureomycin was given in decreasing dosage. Bullae became somewhat more frequent. Sulphapyridine, 1 g. thrice daily, and liquor arsenicalis, up to 20 min. (1.2 ml.) thrice daily, failed to prevent the occasional eruption of blisters which, at this time, were clinically typical of dermatitis herpetiformis. All active lesions had completely subsided by October 19 while under out-patient treatment with liq. hydrarg. perchlor.

When last seen (January 25, 1951) the patient was free from skin lesions.

Case 8. Dermatitis Herpetiformis

An Englishwoman aged 77 had a bullous eruption which started in June, 1950. On admission to hospital on August 4, 1950, there was a generalized eruption similar to that in Case 7. Biopsy revealed subepidermal vesicles with no acantholysis. Tzanck's test showed no pemphigus cells.

Aureomycin, 2 g. daily (loading dose 4 g.), was given from August 4 to 15 and the blisters entirely disappeared.

Two months later vesicles typical of dermatitis herpetiformis developed on the trunk and limbs and were then controlled by the administration of liquor arsenicalis. She was well in February, 1951.

Comment

Pemphigus Vulgaris

All three of these cases presented the typical clinical appearances of pemphigus vulgaris, and in Cases 2 and 3 the diagnosis was confirmed by biopsy. In the latter we have attached importance to the presence of intra-epidermal bullae and acantholysis, indicating a lack of cohesion between cells of the Malpighian layer of the epidermis (Civatte, 1943; Rook and Whimster, 1950). The test elaborated by Tzanck (1948) depends upon the finding of detached epithelial cells showing nuclear degeneration and shrinkage of the cytoplasm in scrapings from the floor of the bullae. Such cells, according to Tzanck, are to be found only in diseases in which acantholysis is present, and the usefulness of his test has been confirmed in this country by Rook and Whimster.

In these three cases a complete or partial abolition of fresh bullae followed so quickly and strikingly after the administration of aureomycin that it was impossible not to receive the strong clinical impression that it was more than coincidence. In Case 1 the eruption was completely abolished and the patient's general condition improved at the same time. In Case 2 the severity of the eruption was repeatedly abated during aureomycin administration, relapsing twice soon after treatment was interrupted. In this case, although the eruption was largely controlled, a corresponding improvement in the patient's general condition did not take place and she appeared to die of the toxæmia and exhaustion which are usual in pemphigus vulgaris.

We must note, however, that owing to nausea and vomiting it was doubtful how much aureomycin was being retained. This complication provided a difficult problem, and we had to choose between a relapse of pemphigus and this distressing gastric upset. Perhaps parenteral administration would have met the difficulty.

In Case 3 the control of the eruption with aureomycin was again very striking, though it is evident that this patient is not cured.

The nature and cause of pemphigus vulgaris is still unknown, and the identification of a virus by Urbach and Wolfram (1936) still awaits adequate confirmation. Spontaneous remissions are a feature of the disease, and it may be that the effect of aureomycin has been only to suppress the eruption until a remission occurs. The existence of the eruption can be largely attributed to lack of cohesion between the Malpighian cells, however this may be caused; it may be that aureomycin has the effect of restoring the cohesion of these cells without necessarily attacking the cause, whether virus or otherwise. This was particularly suggested in Case 3: before treatment was started large flaccid blisters could be pressed out and made to extend themselves without

breaking. The blisters which appeared during aureomycin therapy were very much smaller, more tense, and, when pressed upon, ruptured without spreading. This observation suggests that aureomycin may restore the cohesion of the Malpighian cells without attacking the underlying cause of the disease. Such an action might be a direct effect on the Malpighian cells, or might result from an alteration of intestinal biosynthesis.

In Cases 1 and 3 aureomycin was continued over a period of many weeks. Chloramphenicol was given only in Case 2, and seemed to have no effect in the dosage employed.

Pemphigus Vegetans

In this disorder, again, spontaneous remissions often occur and response to various forms of treatment has occasionally been reported. In Case 4 chloramphenicol was started at a time when the eruption was steadily becoming worse; clinical improvement took place within a few days and the production of pustules was immediately halted. A striking feature was the fall in blood eosinophilia from 3,000 per c.mm. to *nil* in the course of two and a half weeks.

In Case 5 response to chloramphenicol was obtained only on the higher dosage of 4 g. daily; the response was then striking. When, after five weeks' treatment, the drug was stopped the condition of the skin slowly relapsed but quickly responded again when the higher dosage of chloramphenicol was resumed. In this case the blood eosinophilia remained unchanged at about 3,000 per c.mm.

Aureomycin was given in Case 5 only in the dosage of 2 g. daily; it may be that in a dosage of 4 g. daily this too would have been effective.

Pemphigus Erythematousus

This patient's eruption was mild and her general condition good. Her response to both aureomycin and chloramphenicol seems to have been favourable. It was not, however, nearly so striking as in most other cases, the improvement taking place much more gradually. We were much less convinced in this case that the patient's improvement was due to the treatment that she had received.

Dermatitis Herpetiformis

We have not used chloramphenicol or aureomycin in the treatment of dermatitis herpetiformis in its ordinary manifestations, although some favourable results have been recorded.

The two cases here were in elderly people whose eruptions resembled clinically those of pemphigus vulgaris but were distinguished by the absence of acantholysis and hence by the absence of pemphigus cells in Tzanck's test. Histologically, the bullae were subepidermal and resembled those of dermatitis herpetiformis. A diagnosis of bullous dermatitis herpetiformis was therefore made, and was supported by the development of the typical lesions of that disease later on. The bullous form of dermatitis herpetiformis may, however, lead to general exhaustion and, in these elderly patients, may well be fatal. In both cases aureomycin treatment was followed within a few days by complete or almost complete cessation of blisters and consequent improvement in the patient's condition. This bullous phase of dermatitis herpetiformis is often unresponsive to arsenic and sulphapyridine, and it seems that aureomycin has the effect of partly controlling the eruption, when it resumes

the more usual features of the disease and may again be controlled with arsenic.

It is interesting to observe that in Case 8 the bullae were at first flaccid and, although they were entirely subepidermal, could be pressed out and made to extend beneath the epidermis. After the administration of aureomycin the vesicles that subsequently appeared were small and tense and could not be pressed out.

Conclusions

In this small series of cases we found that aureomycin appears to influence the production of bullae in both pemphigus vulgaris and bullous dermatitis herpetiformis. The virus aetiology of these two diseases is still unproved, and it may be that the action of aureomycin is not against an infective agent but is a direct effect on the cohesion of the cells of the epidermis.

In pemphigus vegetans, in which bullae are much less prominent, chloramphenicol appeared to be effective in melting away the vegetating masses at a surprising speed. In one of these cases, on the other hand, aureomycin seemed to be ineffective in the dosage given.

We have adopted 2 g. daily (0.25 g. three-hourly) as our standard dosage, with an initial loading dose of 4 g. In some cases, however, it seemed advantageous to give double this standard dose. Vitamin supplements were given by mouth during the period of antibiotic administration.

While response to treatment was usually obtained within a few days, we have formed the opinion that these antibiotics need to be continued for at least a month to six weeks if early relapse is to be avoided, and it seems that some of the unsuccessful trials of these drugs which have been reported may be due to dosage either too small or continued for too short a time.

None of our cases were complicated by much secondary infection. Treatment was followed by a suppression of the primary lesions of the disease, an effect which was clearly not due simply to removal of secondary sepsis.

Supplies of these drugs have not as yet been sufficient for us to determine the value of smaller maintenance doses as a means of preventing eventual relapse.

REFERENCES

- Barber, H. W., and Yorke, A. (1950). *Proc. roy. Soc. Med.*, **43**, 555.
 Beinhauer, L. G. (1950). *Arch. Derm. Syph., Chicago*, **62**, 290.
 Bettley, F. R. (1950). *Lancet*, **1**, 66.
 Brainerd, H., Lennette, E. H., Meiklejohn, G., Bruyn, H. B., jun., and Clark, W. H. (1949). *J. clin. Invest.*, **28**, 992.
 Civate, A. (1943). *Ann. Derm. Syph., Paris*, 8e Sér., **3**, 1.
 Combes, F. C., and Canizares, O. (1950). *Arch. Derm. Syph., Chicago*, **62**, 786.
 Degos, R., Garnier, G., and Caron, J. (1949). *Bull. Soc. franç. Derm. Syph.*, **56**, 490.
 Graciansky, P. de, and Hardouin, J. P. (1949). *Ibid.*, **56**, 490.
 Mathieu, P. L. (1950). *R. I. med. J.*, **33**, 24.
 Philip, A. J. (1950). *Urol. cutan. Rev.*, **54**, 222.
 Robinson, H. M. (1950). *Arch. Derm. Syph., Chicago*, **61**, 384.
 — Robinson, H. M., jun., and Robinson, R. C. V. (1949). *J. invest. Derm.*, **13**, 9.
 Rook, A. J., and Whimster, I. W. (1950). *Brit. J. Derm. Syph.*, **62**, 443.
 Shaw, C. (1950). *J. invest. Derm.*, **14**, 3.
 Spink, W. W., and Yow, E. M. (1949). *J. Amer. med. Ass.*, **141**, 964.
 Tzanck, A. (1948). *Ann. Derm. Syph., Paris*, 8e Sér., **8**, 205.
 — and Meyer, B. (1949). *Bull. Soc. franç. Derm. Syph.*, **56**, 431.
 Urbach, E., and Wolfram, S. (1936). *Arch. Derm. Syph., Chicago*, **33**, 788.