# ANTIHISTAMINES IN NON-URTICARIAL DERMATOSES, AND A RETRIAL OF ANTIHISTAMINE IONTOPHORESIS

BY

P. INMAN, M.D., M.R.C.P.

AND

I. CAMPBELL COWAN, M.D., B.Sc.

*(From the Sunderland Skin Clinic)*

In itching dermatoses other than urticaria and angioneurotic oedema oral treatment by the antihistamine drugs is attended by scant success. What slight improvement results is no greater than might be expected from the sedative action of the drugs alone. From America there are conflicting reports of the results of the use of antihistamine ointments. Thus Madden (1950) reports that of 141 patients with various dermatoses who were treated by phenindamine ("thephorin") ointment, 90% experienced relief or complete cure of the itching, and 5% were made worse. Wooldridge and Joseph (1949) report favourably on the use of phenindamine phosphate in ointment form, and consider that this substance penetrates the skin better than does diphenhydramine hydrochloride ("benadryl") or tripelennamine hydrochloride ("pyribenzamine"). On the other hand, Baldridge (1951), using phenindamine ointment on 41 clinically controlled cases, found that a 5% ointment produced no more relief from itching than did either of the ointment bases used—"carbowax 1500" and a vanishing-cream base. Furthermore, Ellis and Bundick (1949), using 5% phenindamine ointment in a carbowax base or as a 5% lotion in treatment of 50 chronic cases of dermatosis, found clinical sensitivity develop in 28% after an average of 50 days' treatment. They attribute the high incidence of sensitivity to the long period of use of the ointments, but they rightly point out that treatment is long-continued in many chronic dermatoses.

Similarly, McGavack *et al.* (1948) treated with benadryl ointment 74 patients suffering from itching dermatoses. They found complete relief from itching in 59.5% and improvement in 24.3%. They state that six patients felt discomfort from the applications—four of a temporary nature, the other two developing a weeping eczematous sensitization. But Perry (1947) found that the local use of benadryl ointment was of no value in neurodermatitis and of debatable value in other diseases.

After the disasters following application of sulphonamides and penicillin to the skin, English dermatologists seem to have made a more cautious approach to topical application of antihistaminics. Thus Warin (1950) stated that he had had little experience of external application of the antihistamine drugs. He presumed their main effect would be through their local analgesic properties. He felt that dermatitis had been provoked or aggravated by their use. Brain (1950) felt that "creams containing the antihistamine substances are occasionally of value, and they may be tried when other attempts at relieving the irritation of localized lesions fail."

Theoretically it is not to be expected that antihistamine therapy will be as effective in the treatment of eczema and dermatitis, where the site of reactivity is the epidermis, as they are in the case of the urticarial group of eruptions, in which the site of reactivity is the dermal papillae. It is probable that the antihistamine drugs act by blocking tissue receptors of histamine. In urticaria the antihistamine drug given orally is able to block the papillary receptors before the histamine from the epidermis is taken up in the papillae. In the case, however, of dermatitis or eczema the histamine is liberated in the target organ, in this case the epidermis, so that the antihistamine drugs will have less opportunity of blocking tissue receptors of histamine. There is, however, evidence that these drugs have a deterrent action on the actual liberation of histamine by allergic and other types of reaction which normally cause its appearance (Dale, 1950). If this is true the antihistamine drugs might be of use, provided they can be introduced into the epidermis.

Peck *et al.* (1950) found that it was possible to make 3 g. of ointment disappear if it was massaged into an area of skin 10 cm. in diameter. They used 2% pyribenzamine hydrochloride in a petrolatum base and rubbed it into normal skin. By estimating the urinary excretion of pyribenzamine they found that no appreciable quantity of the substance had penetrated the normal epidermal barrier. The same workers repeated the rubbing of ointment over areas of skin which were affected by dermatitis. They found that in a patient suffering from contact dermatitis 2% of the pyribenzamine contained in the ointment was excreted in the urine. They concluded that topical applications of antihistaminics readily found their way through the damaged epidermis, and seemed to be the logical mode of administration of antihistaminics for the treatment of dermatitis. Aaron, Peck, and Abramson (1948), however, state: "Recently ointments containing histamine antagonists for use in dermatitis have been under study. The results were not satisfactory in most instances." Possibly part of the explanation of the failure of the antihistamine ointments is to be found in the violence which is required to cause the antihistamine substances to penetrate the epidermis. Thus it is not surprising that any topical therapy which requires rubbing into areas of dermatitis for five minutes will do more harm than good. In view of this it was felt that a retrial of antihistamine iontophoresis as performed by Aaron, Peck, and Abramson would be worth while, since this method would ensure penetration of the epidermis by the antihistamine compound without the trauma of the rubbing required with the use of antihistamine ointments.

### Choice of Antihistaminic Substance for Iontophoresis

Shelley, McConahy, and Hesbacher (1950) introduced by iontophoresis nine antihistaminic compounds into the skin of the back of five normal male subjects. Five minutes later histamine was introduced iontophoretically into the test areas. By the grading of the whealing so produced they assessed the efficiency of the antihistamines under test. They found pyribenzamine, "diatrin," and mepyramine hydrogen maleate ("neoantergan," "anthisan") the most effective in histamine wheal suppression. They quote a similar study by Rasmussen (1949), who found anthisan, promethazine hydrochloride ("phenergan"), and pyribenzamine the most active. Since no compound was found more active than pyribenzamine it was selected for clinical retrial, after the method of Aaron, Peck, and Abramson.

### Selection of Cases

It was felt that only localized areas of skin were suitable for treatment, so that cases of extensive dermatitis were excluded from the test. So far as was possible, cases of

considerable chronicity were chosen, since a beneficial effect on a dermatosis of recent origin would be less significant. Very acute or weeping eczemas were excluded, because Aaron, Peck, and Abramson (1948) report that their patients experienced a burning sensation about one hour after treatment.

## Method

A single thickness of lint soaked in a 5% solution of pyribenzamine was placed in contact with a pliable zinc anode cut to the shape of the lesion, and both were then covered by a pad of turkish towelling soaked in 2% saline. The anode so constituted was kept in place by rubber bandages and sandbags. The smallest electrode used was 15 cm.$^2$ and the largest 100 cm.$^2$ The indifferent electrode was generally attached to the sacrum. The current density varied between 0.08 and 0.25 mA per cm.$^2$ Whereas Aaron, Peck, and Abramson employed daily treatments of five minutes for seven to ten days, treatment three times weekly was preferred. Also, the duration of treatment was not limited to five minutes, but in most cases was gradually increased up to a maximum of 20 minutes.

## Results

The results are listed in the Table. Improvement is classified as subjective and objective: 0=no improvement; +=slight improvement; ++=moderate improvement; +++=great improvement; ++++=complete absence of itching or complete disappearance of visible lesions. If the patient was inconsistent in his statements or the estimate of improvement differed between us the least estimated improvement was tabulated.

Of the 20 cases listed 19 were very itchy lesions and one (Case 10) never had irritation. Of these 19, nine were either completely relieved of irritation or nearly so, one was moderately relieved, and in one (Case 17) it was not possible to evaluate the itching sensation. The remaining eight cases were not materially relieved of itching. In Case 15 the itching was worse after treatment and the skin looked worse. This patient, a man with undescended testicles and an unusual home environment, had eczema with marked endocrine defect. Case 1, lichen sclerosus et atrophicus, in which the diagnosis was confirmed by biopsy, was unusual in the intensity of the vulval itching, which had for some months almost driven her to distraction. It had resisted all the usual treatments except *x*-ray therapy, which was regarded as unsuitable for such an atrophic condition. Of the 20 cases, only five were much improved objectively, five others being moderately improved, and one made worse.

*Toxic Effects.*—Only Case 7 complained of an uncomfortable burning sensation about three-quarters of an hour after each treatment. There were no other toxic effects in this series.

*Follow-up.*—These cases were followed up some 12 to 18 months after the course of pyribenzamine iontophoresis. Of the 10 cases which had been improved by the pyribenzamine treatment four have remained entirely free from symptoms without further treatment (Cases 4, 5, 12, and 19); five (Cases 1, 3, 6, 8, and 14) relapsed slightly but remained substantially better than before the treatment; one (Case 16) relapsed absolutely. Case 17, in which the itching sensation had not been assessable, has remained entirely free from skin eruption without any further treatment. Of the eight cases not improved by the treatment one (Case 18) showed much improvement after a second course of the pyribenzamine iontophoresis; one was fatal (Case 11—carcinoma of the lung); three have remained unchanged in spite of further and different treatments (Cases 7, 13, and 20); and three (Cases 2, 9, and 15) have been cleared or greatly improved by other means, including prolonged in-patient treatment in Cases 9 and 15. The case of dermatitis repens (Case 10) has somewhat improved following many other and varied treatments.

## Comment

Of the 20 cases treated by pyribenzamine iontophoresis Case 1 (lichen sclerosus et atrophicus) is probably an organic skin disease.

*Table of Results*

| Case No. | Sex and Age | Type and Duration of Skin Lesion | Treatment before Iontophoresis and its Result | No of Treatments | Improvement | |
|---|---|---|---|---|---|---|
| | | | | | Subjective | Objective |
| 1 | F 59 | Lichen sclerosus et atrophicus chest and vulva, with severe vulval itch for 4 months | Failure of rest, sedatives, tar, and carbolic lotions to give any relief | 15 | +++ | 0 |
| 2 | F 47 | 15 years' 4½ by 3½ in. (10·3 by 8·8 cm.) patch eczema outer right ankle | Failure of internal saphenous ligature and injection of moderate calf varicosities. Failure of subsequent *x*-ray therapy and usual applications | 13 | 0 | 0 |
| 3 | F 64 | 15 years' 3 by 4 in. (7·5 by 10 cm.) patch of thickened neurodermatitis below left knee | None known | 12 | +++ | ++ |
| 4 | F 34 | 3 years' lichenified eczema right supraclavicular area and right side neck | *X*-ray therapy with sedatives and antipruritics cleared it temporarily; recurrence 5 months later | 7 | +++ | +++ |
| 5 | F 53 | Prurigo of inner thighs and groins, with high blood pressure | Temporary clearance with *x*-ray therapy and applications. Recurrence | 19 | +++ | ++++ |
| 6 | F 32 | Right supraclavicular neurodermatitis. 9 months | None | 14 | ++ | ++ |
| 7 | F 13 | 4 years' patch infected recurrent eczema inner wrist | Gentian violet ointment | 11 | 0 | 0 |
| 8 | F 37 | 3 years' neurodermatitis of nape | None | 14 | ++++ | +++ |
| 9 | M 55 | Chronic patch eczema back of left leg "present most of his life" | None but biopsy, first performed to confirm diagnosis | 9 | + | 0 |
| 10 | M 44 | Dermatitis repens left lower leg. Some months | Oral sulphonamides and parenteral penicillin besides usual skin antiseptic applications | 13 | — | ++ |
| 11 | M 58 | 5 years' thickened scrotal eczema | Many and varied over 2 years without success | 15 | 0 | 0 |
| 12 | M 43 | 15 years' continuous pubic neurodermatitis | Partial temporary relief by *x*-ray therapy followed by relapse | 13 | +++ | +++ |
| 13 | M 38 | 20 years' patch of eczema behind left knee | None | 15 | 0 | + |
| 14 | M 41 | 5 years' symmetrical thickened eczema about upper end of intergluteal cleft | Recurrence 6 months after *x*-ray therapy | 22 | +++ | ++ |
| 15 | M 38 | 10 by 5 in. (25 by 10 cm.) left upper calf, lichenified thickened patch eczema some months | Only temporary relief from itching by *x* rays | 4 | Worse | Worse |
| 16 | M 29 | 8 months' seborrhoeic folliculitis of nape | None | 12 | ++++ | 0 |
| 17 | M 8 | Patchy excoriated eczema inner and outer left ankle 3 months | None | 24 | ? | +++ |
| 18 | M 30 | 3½ years' pruritus ani; anal skin white, thick, and sodden | *X*-ray therapy had produced improvement with lotion and advice | 23 | ++ | 0 |
| 19 | M 72 | 6 months' papular eczema of wrist following scald | | 20 | ++++ | ++ |
| 20 | M 41 | 9 weeks' pruritus ani with anal skin tags and some stenosis following pile operation | None, except stopping of liquid paraffin without improvement | 13 | + | + |

In assessing the prognosis in any case of eczema or other functional itching skin disorder a large number of factors require consideration. Factors prejudicial to recovery might be grouped thus:

1. *Psychological.*—Domestic disharmony, frustration, or unhappiness at work. Overcrowded housing conditions and friction with "in-laws." Overwork, worry, insomnia, compensation disputes.

2. *General.*—Hypertension, anaemia, dyspnoea from chronic bronchitis, emphysema, or other cause. Alcoholism. Poor renal function as in prostatic obstruction and other states of sub-health. Faulty nutrition. Bad heredity.

3. *Endocrine State.*—Unfavourable influence of puberty and menopause.

4. *Chronicity of the Lesions.*—A dermatosis of many years' duration is likely to be more intractable than one of months or weeks.

5. *Local Factors* (e.g., xerodermia or hyperidrosis).—Haemorrhoids or fistula in pruritus ani, ankle oedema due to varicose veins, deep thrombosis or other cause in leg eczema. Perniosis. Impossibility of avoiding local allergic contacts.

6. Unwillingness or inability to carry out exact treatment.

In attempting to estimate the worth or otherwise of any therapy in these conditions much reliance must be placed on clinical judgment, since cases exactly comparable in every respect with regard to such factors as those mentioned above are not available.

## Summary and Conclusion

Although antihistamine ointments can be absorbed when massaged into areas of dermatitis the friction and trauma of the rubbing may make the dermatitis worse. Their use is therefore likely to be limited, and any beneficial effect is probably due to their gentle application as a surface analgesic. Since they are also potent sensitizers they should be used, for short periods only, on localized areas of skin. They are seldom used in the Sunderland Skin Clinic, and several cases of dermatitis due to them have been encountered.

The introduction of antihistamines into the skin by iontophoresis can be brought about without the trauma and friction necessary to introduce the ointment. The method is free from toxic reactions, and for localized areas of chronic dermatitis or pruritus may have a useful though limited role.

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Two hundred years ago on May 19 Antonio Scarpa, the Italian anatomist and surgeon, was born. He studied under Morgagni and others at Padua, and became an expert anatomist. Soon after obtaining his degree in medicine he published an important work on the ear, in which he recorded his discovery of the membranous labyrinth. During a visit to London he worked with Pott and the Hunters. As professor of anatomy and surgery at Pavia he built his reputation as the greatest Italian anatomist and surgeon of his century. His *Tabulae Neurologicae*, 1794, with beautiful drawings by Scarpa himself, showed him to be one of the best of those medical men who have illustrated their own works. He was the first to tie the femoral artery for popliteal aneurysm. Scarpa was blind for the last few years of his life and died on October 31, 1832.

# A CASE OF CONFLUENT CHICKEN-POX WITH HAEMORRHAGIC SYMPTOMS

BY

J. PICKFORD MARSDEN, M.D., D.P.H.

AND

W. J. COUGHLAN, M.B.

*(From the Infectious Diseases Unit, River Hospitals, Dartford, Kent)*

The following is a record of a case of chicken-pox of exceptional severity which exhibited a confluent haemorrhagic eruption and a severe leucopenia. Recovery followed treatment with "aureomycin."

## Case Report

The patient was a man aged 40, hitherto in good health. On July 21 a small boy arrived to stay in the patient's house, but was found to be suffering from chicken-pox and returned to his own home on July 25. So far as is known there were no unusual features about this attack. Two children of our patient, aged 10 and 4 years, developed chicken-pox about August 3. We are informed that each experienced a mild attack and made a rapid recovery. The patient felt unwell on August 4 and a rash began to appear next day. When first seen by his doctor, on August 7, "he had a very extensive varicella rash and what looked like a follicular tonsillitis": he was febrile, and was sent home to bed and put on sulphonamides. On August 9, as he was vomiting after a restless night, the drug was omitted. The temperature then was 101° F. (38.3° C.). At night he was kept awake by persistent hiccup. On August 10 his temperature had risen still further and the rash began to show a purpuric element: 400,000 units of penicillin was given. Hiccup returned at night. On August 11 aureomycin therapy was started (0.5 g. six-hourly) and admission to hospital was sought because of the severity of the illness and the need for investigation of the haemorrhagic symptoms. Attempts to obtain suitable hospital accommodation nearer his home having failed, we agreed, on his doctor's advice, to admit him to our unit, although this entailed a journey of some 50 miles (80 km.) up from the country.

On arrival the patient was found to have an extremely profuse eruption (Figs. 1 and 2), confluent over the face and on parts of the trunk, quite generalized, and exhibiting no selectivity except that the profusion was greatest on the trunk and face. The rash generally showed purpuric staining, but there was, at this stage, no free bleeding into any of the many large superficial vesicles. The rash was mixed as regards age and size of its elements: it was pustular on the face, of which there was pronounced swelling. A profuse enanthem was present in the mouth and fauces, and there were lesions also on the conjunctivae. The patient felt weak and tired, the pulse was running, some rhonchi were

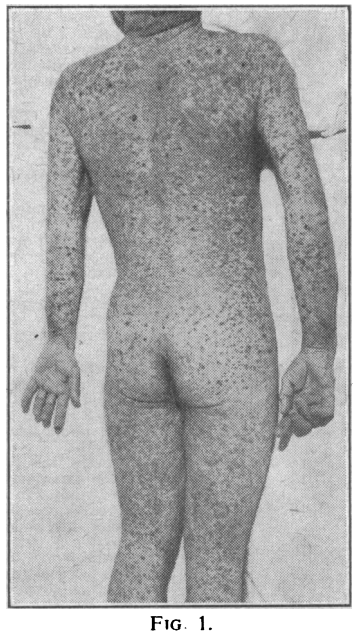

FIG. 1.