NICOTINIC ACID THERAPY OF DERMATITIS HERPETIFORMIS*

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In 1944 one of us (H. H. J.) was informed by a patient, admitted for other than cutaneous disease, that he had suffered with dermatitis herpetiformis for many years. However, at this admission the observed lack of symptoms in the patient was due to self-medication with nicotinic acid. He stated that each time he ceased taking the vitamin the symptoms of dermatitis herpetiformis recurred and upon resuming the nicotinic acid the pruritus and cutaneous lesions subsided.

Since the medications hitherto employed for dermatitis herpetiformis have been either only partially successful or fraught with hazard, the report of striking benefit from nicotinic acid seemed worth further study. This report summarizes experience with nicotinic acid in the therapy of 12 cases of dermatitis herpetiformis.

Case I: M. H., a white male, aged 56, had suffered from a moderate dermatitis herpetiformis for three years. There were vesicles with an erythematous base on the extensors of the forearms and the legs. There was mild hyperpigmentation. A hemogram revealed 18% eosinophilic polymorphonuclear leucocytes. The oral administration of niacin in 0.05 Gm. tablets three times daily after meals and two tablets at bed time controlled the pruritus and prevented the appearance of vesicles. An interim trial of niacinamide in the same dosage failed to control the condition. Therefore, he was instructed to resume niacin for constant use.

Case II: H. P. H., a white male aged 52, had suffered from dermatitis herpetiformis for two years. A hemogram showed 3% eosinophilic leucocytes. Sulfapyridine was given for eight days with moderate effect on the dermatitis herpetiformis but with prompt recurrence of symptoms. Niacin 0.05 Gm. three times daily after meals and 0.1 Gm. at bed time then brought about complete remission. Niacinamide was given with partial recurrence. He has taken niacin for over a year, and remains free from lesions.

Case III: J. W., a white female aged 63 first developed dermatitis herpetiformis in June 1947. There was a spontaneous remission from September to January 1948. The recurrence was severe with bullous lesions on the trunk and extremities, and vesicles on the face, scalp, eyelids, and in the oral cavity. The condition slowly progressed to generalization.

On March 6, 1948 the hemogram showed an increased total leucocyte count of 26,200. The differential count revealed 23% eosinophilic cells. Niacin in doses of 0.15 Gm. four times daily was given throughout the next four weeks. Pyribenzamine was also given a few days later for any antipruritic effect it could contribute. There was slight improvement. During the fourth and last week of her hospital stay, sulfapyridine 0.5 Gm. four times daily was administered with further improvement, but the remission was incomplete. There were vesicles present about the ankles on the day of discharge.

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Case IV: J. W., a white female age 44 was seen on November 6, 1943 complaining of a pruritic eruption of 4 months duration. There was involvement of the left chest, the submammary regions, the extensor of the forearms, each upper shoulder, the lower buttocks and the knees. The primary lesion was a superficial, clear, tense vesicle. The diagnosis was dermatitis herpetiformis.

Without treatment the disease waxed and waned over the next 4½ years until May 20, 1948 when niacinamide 0.05 Gm. three times daily and 0.1 Gm. at bed time was prescribed. There was no change during the next 10 days of this medication. On June 1, 1948 niacin in the same dosage was started. Observation on July 1, 1948 showed that the process was controlled by niacin in 0.05 Gm. doses. On March 24, 1949 the disease is in remission without the use of niacin.

Case V: P. B., (a patient of Dr. G. M. Stroud), a white male aged 34, was seen in August 1947 with an eruption of grouped vesicles. The lesions were located on the neck, arms, knees, and sacral area. There was much pruritus. The diagnosis was dermatitis herpetiformis. The oral use of sulfadiazine for 11 days produced slight improvement which endured for only five days. Sulfathiazole was taken for five days with no effect. Niacin 0.1 Gm. four times daily produced improvement in two days. Complete control of the eruption was maintained for ten months while the patient continued on niacin therapy. At our insistence he substituted niacinamide in the same dosage. In 48 hours he suffered a relapse of moderate severity which continued until he resumed the niacin.

Case VI: G. P., (a patient of Dr. G. M. Stroud) a white male aged 23, had a pruritic vesicular eruption of 3½ years duration. A hemogram revealed 4.5% eosinophilic polymorphonuclear leucocytes. The diagnosis was moderate dermatitis herpetiformis. Treatment was begun with niacinamide. After two weeks trial of this drug, niacin was prescribed in doses of 0.05 Gm. three times daily after meals and 0.1 Gm. at bed time. The improvement was definite in one week. After trial of various doses to avoid the flushing reaction a dose of 0.075 Gm. four times daily was adopted with almost complete control.

Case VII: I. M. W., a white female aged 26, had an eruption since age 4. It had been diagnosed as dermatitis herpetiformis repeatedly. Previous therapy with liquor potassii arsenitis and sulfapyridine gave only temporary relief. There was a complete remission during a pregnancy. She stated that "the day after delivery pruritus and lesions returned". Examination showed grouped erythematous papules on an edematous base located on scapular areas, above the buttocks and on the elbows and abdomen. Nicotinic acid in doses of 0.1 Gm. after meals produced a good initial response, but since some lesions continued to appear it was increased to 0.15 Gm. and finally to 0.2 Gm. after meals. This resulted in partial control of the disease.

Case VIII: H. P., a white male had dermatitis herpetiformis of 4 years' duration. Examination on November 18, 1948 showed grouped excoriated papules on the elbows, knees, over the shoulders and in the sacral region. Niacin 0.05 Gm. four times daily was taken for 12 days with a marked reduction of the itching and burning and a resolution of existing blisters. When niacin was reduced to 0.025 Gm. four times daily a relapse occurred. This was controlled by increasing the niacin to 0.05 Gm. four times daily and by adding 0.1 to 0.2 Gm. of Pyribenzamine daily. When the total dose of niacin is below 0.1 Gm. per day, the patient notes the presence of a few lesions.

Case IX: J. E. H. (Drs. H. N. Cole, J. R. Driver and H. N. Cole, Jr.) a white male aged 17, was seen in December 1947 for itching and burning of the skin which first appeared in April 1947. Examination revealed papulo-vesicles, crusts and scars over the face, trunk, knees, upper arms, and thighs. The process was extensive over the back and on the genitalia. There was also some pigmentation. The diagnosis was dermatitis herpetiformis. Sulfapyridine 1.0 Gm. three times daily was prescribed and for local application 10% Zetar and bismuth tribromphenate in calamine liniment N. F. When seen in September 1948 he stated he had received no relief from sulfapyridine, but the local treatment relieved the itching. The eruption was still extensive on the thighs, over back, sternum, face and under the arms. He was advised to continue the local treatment and in addition, solution of arsenous

acid, 5 drops, three times daily was prescribed. When he reported gastric reaction to the arsenous acid, Pyribenzamine 0.05 Gm. three times daily after meals and at bed time was administered but with little effect.

On December 13, 1948 niacin 0.05 Gm. three times daily and at bed time was taken with prompt remission of the pruritus and the active cutaneous lesions. When niacinamide was substituted for two weeks the condition recurred. Niacin was resumed and on March 9, 1949 there was 50% remission of the cutaneous lesions and complete control of the pruritus.

Case X: J. M. W., (Drs. H. N. Cole, J. R. Driver and H. N. Cole, Jr.) a white female aged 48, was first seen in August 1944 with a history of a pruritic eruption for four years, previously diagnosed by Dr. Wm. H. Guy, Pittsburg, Pa. as dermatitis herpetiformis. Examination revealed practically the entire body to be covered with numerous pigmented and depigmented scars and many scattered vesicular and crusted lesions. The diagnosis was dermatitis herpetiformis.

Sulfapyridine was prescribed. Two months later she developed a different type of eruption. It was felt that it might be due to sensitivity to sulfapyridine, therefore this medica-

TABLE I

Summary of niacin effect in 12 cases of dermatitis herpetiformis

SEX	DURATION OF SYMPTOMS	SUPPRESSION WITH NIACIN		
		Complete	Partial	None
1. Male	3 years	X		
2. Male	2 years	X		
3. Female	1½ years			X
4. Female	4½ years	X		
5. Male	3 months	X		
6. Male	3½ years		X	
7. Female	22 years		X	
8. Male	4 years	X		
9. Male	1½ years		X	
10. Female	8 years			X
11. Male	1 year		X	
12. Female	5 years	X		

tion was discontinued. With local x-ray therapy and solution of arsenous acid there was improvement but recurrence occurred as soon as this therapy was discontinued. She was seen again on March 25, 1949. During the past month she has been taking niacin 0.05 Gm. four times daily and noted "marked feeling of heat". She did not think that the pruritus or eruption was any better. There was an extensive papular excoriated process. Solution of arsenous acid, 3 drops to be taken four times daily was prescribed again.

Case XI: C. R. U. (Drs. H. N. Cole, J. R. Driver and H. N. Cole, Jr.) a white male aged 32, was seen on February 24, 1949 with a history of the onset of a pruritic eruption on the trunk in March 1948. Since that time the eruption has nearly cleared on 3 occasions, only to recur again. Examination revealed a grouped erythematovesicular symmetrical eruption involving the axillae, neck, antecubital fossae, anterior chest, abdomen, buttocks and lateral aspect of the thighs. Areas of scarring and pigmentation were present. The diagnosis was dermatitis herpetiformis.

Treatment consisted of x-ray therapy 38r to eight areas, potassium permanganate compresses twice daily and niacin 0.05 Gm. four times daily. When seen on March 23, 1949 great improvement was noted. He has had some flushing and dizziness from the niacin.

Case XII: L. S. A. (Drs. H. N. Cole, J. R. Driver and H. N. Cole, Jr.), a white female, had dermatitis herpetiformis for 5 years, and had not responded to any previous therapy.

Examination on March 28, 1949 showed a scattered but diffuse eruption over the entire trunk and extremities with new-formed and old vesicles, many of them arranged in annular configuration. There were numerous scratch marks and extensive pigmentation and scarring.

Niacin was prescribed in small doses, later increased to 0.1 Gm. four times daily. When seen 3 weeks later the skin showed complete remission of active lesions and she was free from itching.

The essential data in regard to these cases is summarized in Table I.

DISCUSSION

Although niacin and its amide have been used in erythema multiforme (Weisberg & Rosen) (1), erythema induratum (Ferreira-Marques) (2), and many pruritic diseases (Ferreira-Marques) (3) no reference to their use in dermatitis herpetiformis was found in the literature.

The medications that have been of definite benefit were the arsenicals and sulfapyridine. The control of dermatitis herpetiformis by sulfapyridine has been reported by Costello (4), Swartz and Lever (5), Barling (6) and others. Since sulfapyridine is strikingly more effective in dermatitis herpetiformis than other more effective antibacterial sulfonamides as sulfanilamide, sulfathiazole and sulfadiazine, it suggests that the action of sulfapyridine in this disease might be other than antibacterial. Costello (7) reported the experience of a young man whose dermatitis herpetiformis was controlled by sulfapyridine. He observed that the sulfapyridine was ineffective and that he had a recurrence of symptoms when paraminobenzoic acid (0.1 Gm. three times a day) was administered. This experience was repeated several times. Andrews remarked (discussion of Costello) (7) that, in addition to the assumption that sulfapyridine may act through its sulfanilyl radical, one must consider that the benefit may come from the pyridine radical.

Niacin is not a specific for dermatitis herpetiformis, but exerts a suppressive effect in approximately half the cases and varying degrees of partial effect in an additional one-third of the cases when given in doses which are able to produce fleeting clinical vasodilatation. We found that niacin amide, which produces no vasodilatation, was relatively ineffective in 6 of the 12 cases. Although one must consider that niacin benefits dermatitis herpetiformis simply through a vascular effect, it is possible that it produces its effect in some other manner such as on the intercellular respiratory enzymes. This possibility is suggested by the fact that sulfapyridine and niacin both contain the pyridine ring, and also by the fact that arsenic preparations and sulfapyridine, two drugs having an empiric effect on dermatitis herpetiformis, are known to exert other pharmacologic effects on the basis of their action on respiratory enzymes.

Further study of other substitution products of nicotinic acid, of drugs containing the pyridine radical and the investigation of unrelated drugs capable of producing vascular dilatation, may provide further information on the observed effect of niacin on dermatitis herpetiformis.

SUMMARY

In a series of 12 patients with dermatitis herpetiformis of various degrees of severity, the oral administration of niacin in doses of 50 to 200 mgm. four times daily relieved the pruritus and improved the cutaneous manifestations.

The disease was completely suppressed in 6 of the cases, partially suppressed in 4. Little or no improvement was observed in two cases. Niacin produced no permanent remissions, but had to be taken in maintenance doses or resumed at the onset of a relapse.

Niacinamide in comparable doses was less beneficial in 6 of the same patients.

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DISCUSSION

Dr. Rudolf L. Baer: Several years ago I discussed with Dr. Oppenheimer of the Ciba Company the difficulties which might arise if sulfapyridine was taken off the market, which appeared to be a definite possibility at that time. I told him that this drug was very important to dermatologists because of its beneficial effects in many cases of dermatitis herpetiformis. He suggested trying nicotinic acid and other chemical relatives of sulfapyridine. Subsequently, I tried niacinamide in a few cases but there was no significant effect from it.

Dr. Stephen Rothman: After we confirmed the observation that sulfapyridine is effective in the management of dermatitis herpetiformis while other sulfa drugs have hardly any effect, Dr. Felsher in our department investigated the effect of other pyridine compounds such as pyridium, nicotinic acid, nicotinamide and pyribenzamine. Although all these compounds had some effect in controlling the eruption and pruritus, none of them matched sulfapyridine. There are five patients now under my observation who refuse to take any pyridine derivative other than sulfapyridine because of the greater efficiency of the latter. Thus it appears that the sulfonamide radical is important in addition to the pyridine ring. It is certainly desirable to search for other effective pyridine compounds

because of the potential toxicity of sulfapyridine. Unfortunately nicotinic acid and nicotinamide have not given quite satisfactory results in our experience.

DR. WALTER LEVER: Dr. Swartz and I showed in a paper published in 1943 (Swartz, J. H. and Lever, W. F.: Dermatitis Herpetiformis, Arch. Dermat. & Syph. **47:** 680, 1943) that sulfanilamide was almost as effective as sulfapyridine in the treatment of dermatitis herpetiformis, although it had to be given in doses about twice as large as those of sulfapyridine in order to be effective. Thus, there is no reason to believe that it is only the pyridine component of sulfapyridine that exerts an effect on dermatitis herpetiformis.

I should like to ask Dr. Binkley one question. How high a dose of nicotinic acid did he give to the two patients who did not respond to this therapy? Adequate dosage seems to be a very important factor in the control of dermatitis herpetiformis. Not infrequently one hears that a patient with dermatitis herpetiformis is not responding to treatment with sulfapyridine. I have not yet encountered any such case; but the dosage of sulfapyridine must be quite high in some patients. For instance, in one of my patients with severe dermatitis herpetiformis 8 Gms. of sulfapyridine daily is required for an adequate control of the eruption. The patient has so far taken this amount of sulfapyridine for almost 2 years.

DR. G. W. BINKLEY: (Closing Discussion) In answer to Dr. Lever, one of the cases I presented in detail perhaps did not have a fair trial with niacin; she objected to the feeling of warmth and flushing. Her dose was only 50 mgms. for a short time. The maximum dose in other cases was 200 mgms. 4 times daily. Two cases reached that dose. The majority maintained comfort and relief of itching on approximately 75 or as low as 50 mgms. We are grateful for Dr. Baer's efforts in regard to the continued availability of sulfapyridine for as you see from our series, nicotinic acid does not control all cases.

Dr. Rothman's experience with pyridium is going to be helpful to us. We plan to try some of these related compounds.

We did not employ Pyribenzamine in our series because the literature to date casts some doubt on its effectiveness in this disease.

In 1947 Osborne, Jordan, and Rausch* reported that Pyribenzamine in doses of 200 to 300 mgm. daily was effective in 3 of 4 patients with dermatitis herpetiformis. The pruritus was relieved and the eruption healed. However, the experience at the Mayo Clinic, as reported by Montgomery in the discussion of this paper, indicated failure in five cases.

* Osborne, E. D., Jordan, J. W. and Rausch, N. G.: Clinical Use of New Anti-histaminic Compound (Pyribenzamine) in Certain Cutaneous Disorders. Arch. Dermat. & Syph. **55:** 309 (March) 1947.