ACRODERMATITIS ENTEROPATHICA, A DISCUSSION AND REPORT OF A CASE SUCCESSFULLY TREATED*

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Acrodermatitis enteropathica, a disease entity first described by Danbolt and Closs in 1942,[1] was reviewed by Dillaha et al[2] in 1953 and, for the first time, successful treatment with Diodoquin was reported. In spite of the fact that it is essentially limited to the pediatric age group, it first appeared in the pediatric literature in 1956 in an article by Vedder[3] in which Diodoquin was again reported effective in relieving the manifestations of the disease. Vedder speculated that once this disease, relatively rare to judge by the number of cases reported (21 at the time of Dillaha's review in 1953), became better known, many more cases would be unearthed. A review of available literature since that time indicates that its appearances are still infrequent, although it is now well established in the dermatology texts[4, 5, 6] and attention has been directed toward it in other pediatric media.[7, 8]

As described, the outstanding signs and symptoms of acrodermatitis enteropathica are cutaneous and are notable for their variety and their distribution. This contributed to the confusion in early reports of the disease since there is, at times, ample reason to confuse it with generalized moniliasis, epidermolysis bullosa or even psoriasis. Typically, the lesions are vesiculopustulobullous plaques, appearing symmetrically, in crops, around the body orifices—notably the mouth and diaper area—plus the neck, the occiput, and the extremities. The trunk per se is not often involved. These lesions may begin to dry and crust in a week or so, with lamellar scaling. At times this process is so marked that the lesions have a distinctly psoriasiform appearance. In the patient to be described below this process was most marked over the extensor surfaces of the elbows and knees, in typical psoriasis fashion. Secondary infection is not infrequent, either bacterial or monilial. In our patient the lesions of the neck

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and in the diaper area had become confluent with an angry red erythema, weeping at times, and with sharply defined, slightly raised margins — lesions quite consistent with what one might expect to find in cutaneous moniliasis.

The other notable cutaneous findings relate to the ectodermal appendages: alopecia of the scalp, eyebrows and eyelids is almost always complete. Involvement of both finger and toenails may produce severe paronychia, with marked dystrophic changes. In addition, the tongue and buccal mucosa may show whitish plaques.

The gastrointestinal tract is the other major system involved. Diarrhea may be almost constant or may accompany exacerbations of the skin manifestations. At times frothy, bulky, foul-smelling stools may occur and present a picture strongly suggestive of the coeliac syndrome. These children are likely to be retarded in their growth and development; this is probably on a nutritional basis secondary to the gastrointestinal symptoms. Although it was not prominent in our patient, it is said [2] that the patient characteristically prefers to hold his head at an angle and face downward. They tend to be irritable and fretful and are sometimes described as withdrawn, although mental development seems to be within normal limits.

Four other features of acrodermatitis enteropathica are seen consistently and are worthy of note in this brief discussion. The onset of symptoms is early, almost always associated with cessation of breast feeding and, where patients are not breast fed, onset may be as early as four weeks of age (see Case 4 of Vedder [3]). The disease is characterized by exacerbations and remissions with cutaneous and gastrointestinal symptoms usually in phase. There is unquestionably a familial tendency. (For an outstanding example, again see Vedder— five of twelve siblings were affected.) Finally, *Candida albicans* is not invariably but very frequently present; on culture it may be obtained either from skin lesions, stools or both.

Attempts to establish the etiology of acrodermatitis enteropathica have been related to some of the various features described above. Brandt [9] suggested early that some unknown factor in breast milk seemed to have a preventive effect since onset usually occurs after weaning, symptoms are relatively mild as long as some breast milk is taken, and remissions could be produced by adding breast milk to the diet of patients.

The role of *C. albicans* has received considerable attention but remains unclear. Dillaha [2] summarizes the discussions, pointing out that the possibility remains that the disease is due to moniliasis in the gastrointestinal tract with an associated id reaction. The variability

in finding *C. albicans* on culturing the lesions, as noted above, is one of the chief sources of confusion. In Dillaha's case he points out that though they were able to eliminate *C. albicans* from the skin by topical therapy, new crops of lesions continued to appear.

An explanation of the pathogenesis of the disease must also take into account the familial nature of the disease as well as the phenomenon described in Vedder's Case 1. This female patient was followed through childhood and into adult life and he reports that all manifestations subsided spontaneously within three weeks after menarche but that after a ten-year remission symptoms reappeared during the third trimester of her first pregnancy, only to disappear again following termination of the pregnancy.

The gradual effectiveness of cortisone acetate, followed by recurrence of the lesions on withdrawal of the drug, as reported in Dillaha's case, offers no clear-cut lead. Neither does the now well established effectiveness of Diodoquin which, interestingly enough, must be given continuously since recurrences also occur promptly following its withdrawal.[3] Just how Diodoquin produces its dramatic results remains to be explained. Its therapeutic reputation is chiefly derived from its effectiveness as an amebecide, though it is also used in the therapy of other protozoan diseases (e. g.: *Trichomonas vaginalis.*) and, topically, in treating fungal infections of the skin. [10] It is practically insoluble in water and therefore is minimally absorbed. Its effect, whatever it may be, must be wrought primarily within the gut itself. It has been suggested by Bloom[11] that it "eliminates the formation of toxic products which otherwise would be absorbed." It would seem reasonable to speculate that if it were effective against *C. albicans* in the gut, the elimination of these organisms might eliminate the source of an id reaction. Dillaha reports that stool cultures from his patient, while negative for *C. albicans* after treatment with Diodoquin, grew other yeasts, and questions whether Diodoquin would selectively eliminate *C. albicans* while allowing other yeasts to grow.

It will be seen from the case report below and from the accompanying figures that our patient presents an almost classical picture of acrodermatitis enteropathica— if so "young" a disease can be said to have a "classical picture." Because the disease remains rare in the pediatric literature and because of our experiences in its therapy we felt this patient's story was worth reporting.

Case Report

N. O., a 10 month old female infant, was brought to the Outpatient Clinic of the Hacettepe Children's Hospital on 21 May 1959.

Her parents complained of skin lesions, present for five months, anorexia and weight loss. The history of these complaints revealed that the skin lesions began when she was five months of age. Erythematous lesions first appeared on the back of the neck, spread rapidly around the neck, over the face and jaws, then appeared over the diaper area, finally the extremities. The lesions, especially those of the face and neck, were occasionally raw and weeping, at other times were crusted over. At this time there was no alopecia and no gastrointestinal symptoms such as diarrhea. In spite of a variety of treatments, the exact nature of which was unknown to the parents, there was no improvement. After about one month, however, the symptoms spontaneously regressed and remained quiescent for approximately one month.

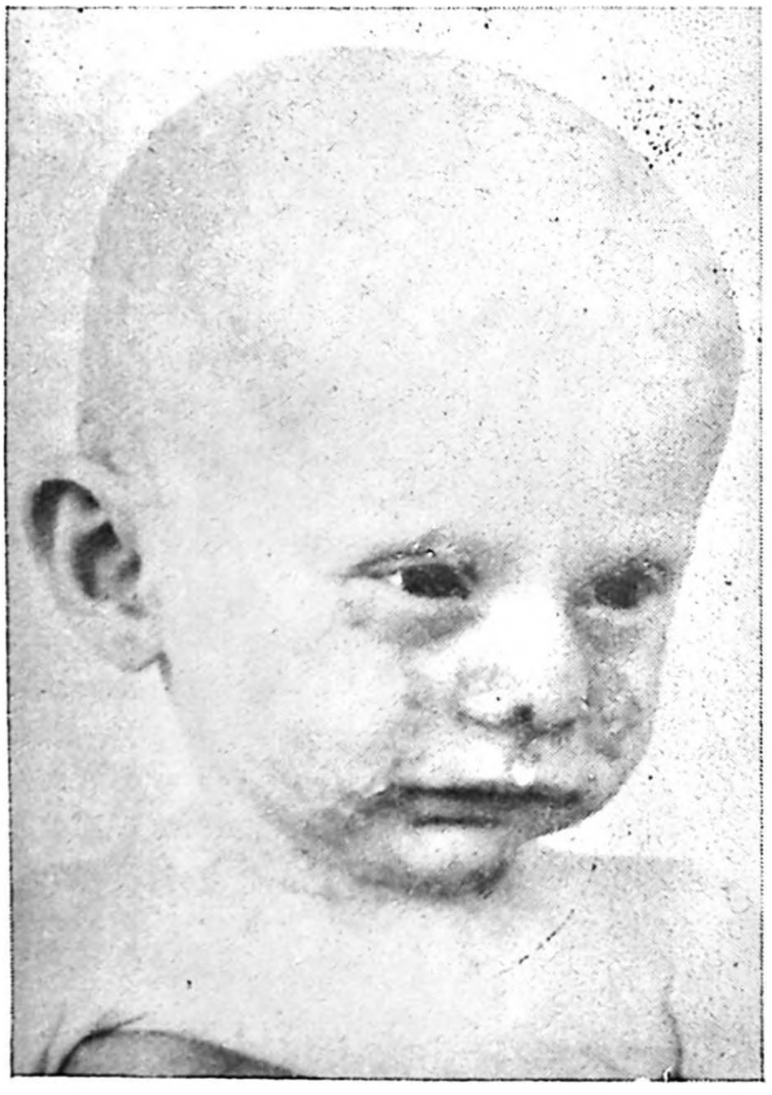


Figure 1. This photograph shows the distribution of the lesions around the mouth and over the face. The alopecia of the scalp, eyebrows and eyelashes is also evident.

At seven months of age a smallpox vaccination was applied and coincident with this the lesions recurred. This time the lesions were more widespread in extent and more severe – that is, there seemed to be more inflammation and, on occasion, more weeping. At this time also, alopecia of the scalp, eyebrows and eyelids appeared. There were, however, no gastrointestinal symptoms during this period. The mother, in fact, reported that the child was frequently constipated. The skin manifestations persisted until admission, varying from time to time in severity, but never clearing completely. During this period further treatment was attempted without avail; again, the parents did not know exactly what was used, although they recalled that Mysteclin was given, one capsule daily for three or four days.

The past history of this child revealed that she was the product of the 4th pregnancy; that pregnancy and delivery were normal. Birth weight was unkown. She was breast fed exclusively until the

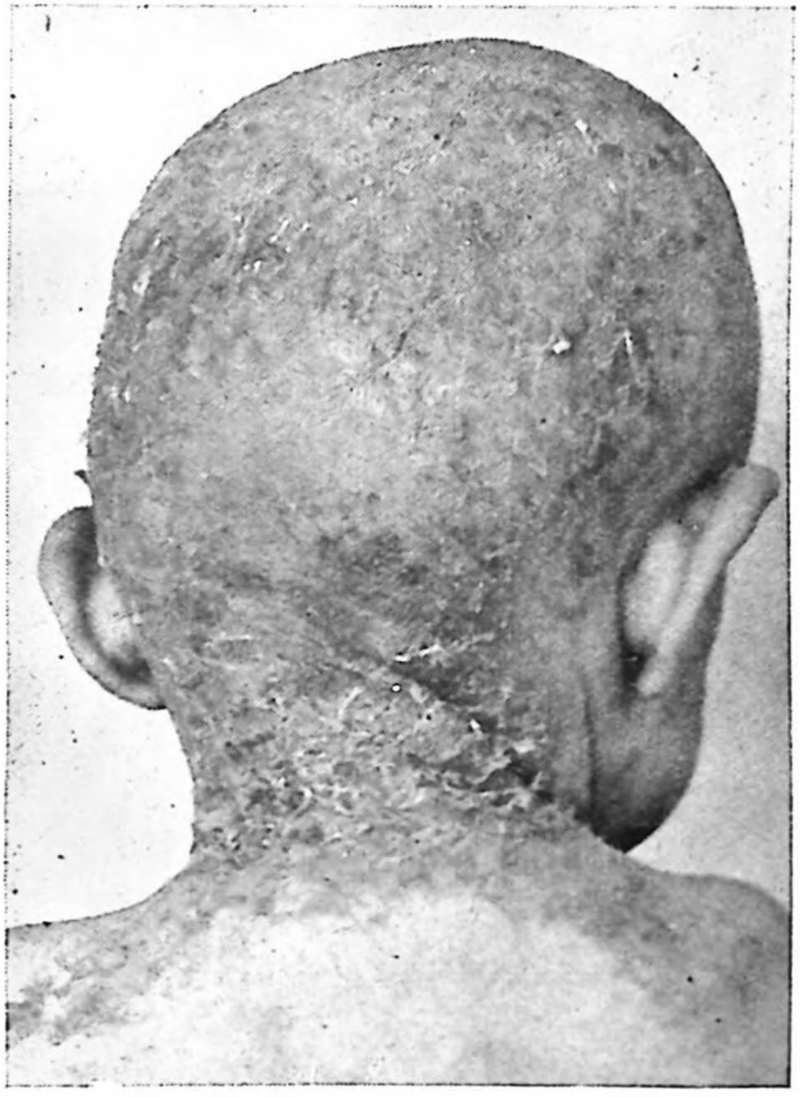


Figure 2. The lesions of the occiput and the back of the neck, characterized by extensive scaling, are shown in this photograph.

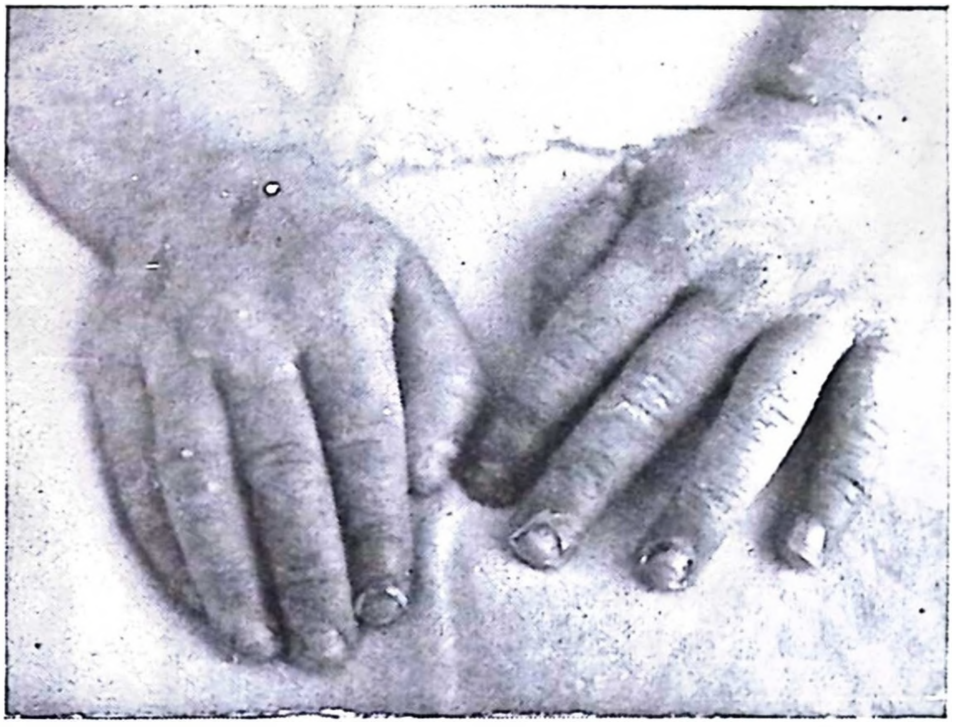
age of 6 months. At that time breast feedings seemed inadequate and yoğurt, cow's milk and biscuits were added to the diet. Growth and development seemed normal to the parents until age 5 months, when growth slowed and she began to gain poorly. She began to sit up at about 6 months of age, but subsequently refused to do so. She has had no illnesses other than the skin lesions.

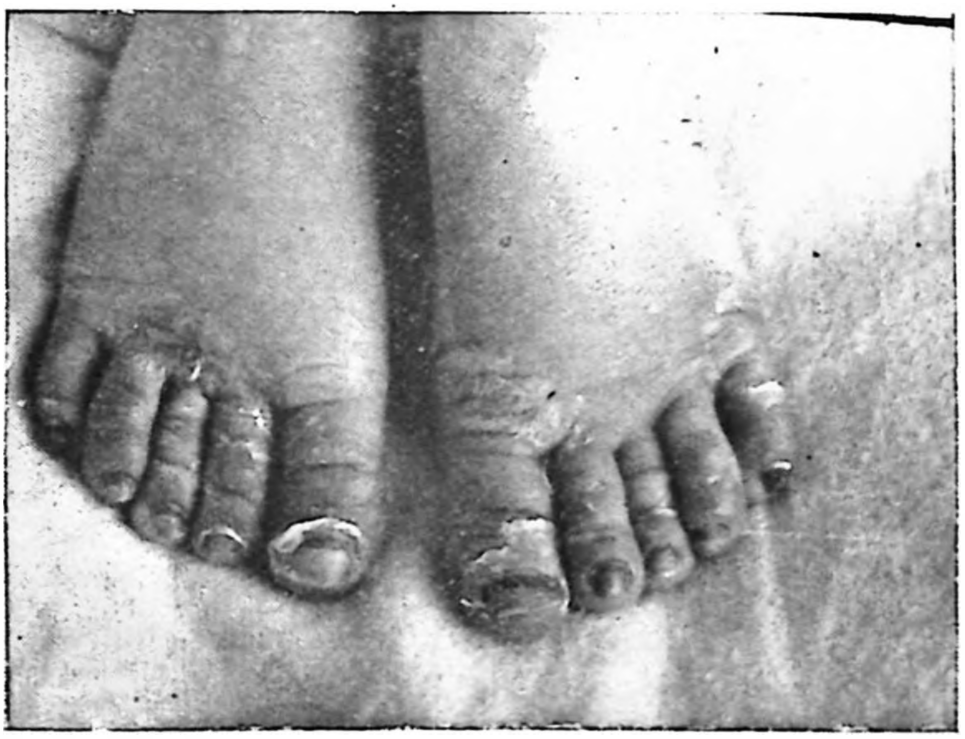
The family history revealed that an older sibling, the product of the first pregnancy, had an illness with the same manifestations as this patient showed and died at around two years of age of the disease or complications thereof. Two other siblings are in good health as are the parents, who are, however, second cousins.

Physical examination on admission revealed a thin, somewhat apathetic female infant who was not especially irritable and seemed in no significant distress. In the sitting position she tended to bend her head forward but there was no particular tendency toward one side or the other. She was 71 cm. in length and weighed 6,150 gm. Vital signs were normal. Significant physical findings were limited to the skin and its appendages. There was almost total alopecia of the scalp, eyebrows and eyelids. Around her mouth, eyes and cheeks were seen irregularly shaped, flat vesiculobullous lesions, some of which were dried and covered with a yellowish crust; there were also simple erythematous macules, up to 1 cm. in diameter. Over the entire occiput, the back of the neck and extending around the neck, collar-like, was one large confluent erythematous lesion with an irregular, sharply defined, slightly raised border. Within this lesion were areas of thickened erythematous skin, areas which were raw and weeping, and areas of prolific scaling and desquamation. A similar extensive lesion covered the perineum and genital area. Over the extensor surfaces of the extremities, symmetrically distributed, were psoriasiform lesions with large thick transluscent scales. The distal phalanges were swollen and erythematous with some scaling. All nails of all four extremities showed irregular, marked thickening with some dystrophic changes and a general appearance of paronychia. Over the right thoracic wall were a few vesiculobullous lesions similar to those on the face. On the palatal mucosa was seen a whitish bulla surrounded by erythema.

Routine examination of the blood and urine revealed no significant abnormalities. An intradermal PPD skin test was negative. Cultures obtained from the lesions of the face, neck, the perineum and the extremities as well as the stool, all grew out *C. albicans*. In addition there were *E. coli* and *A. aerogenes* in the stool.

On the fourth day of admission there was rather sudden onset of diarrhea of unknown etiology producing mild dehydration and necessitating intravenous fluid therapy. Immediately thereafter there was definite improvement in the appearance of the lesions with a decrease in erythema, drying out of weeping lesions and an increase

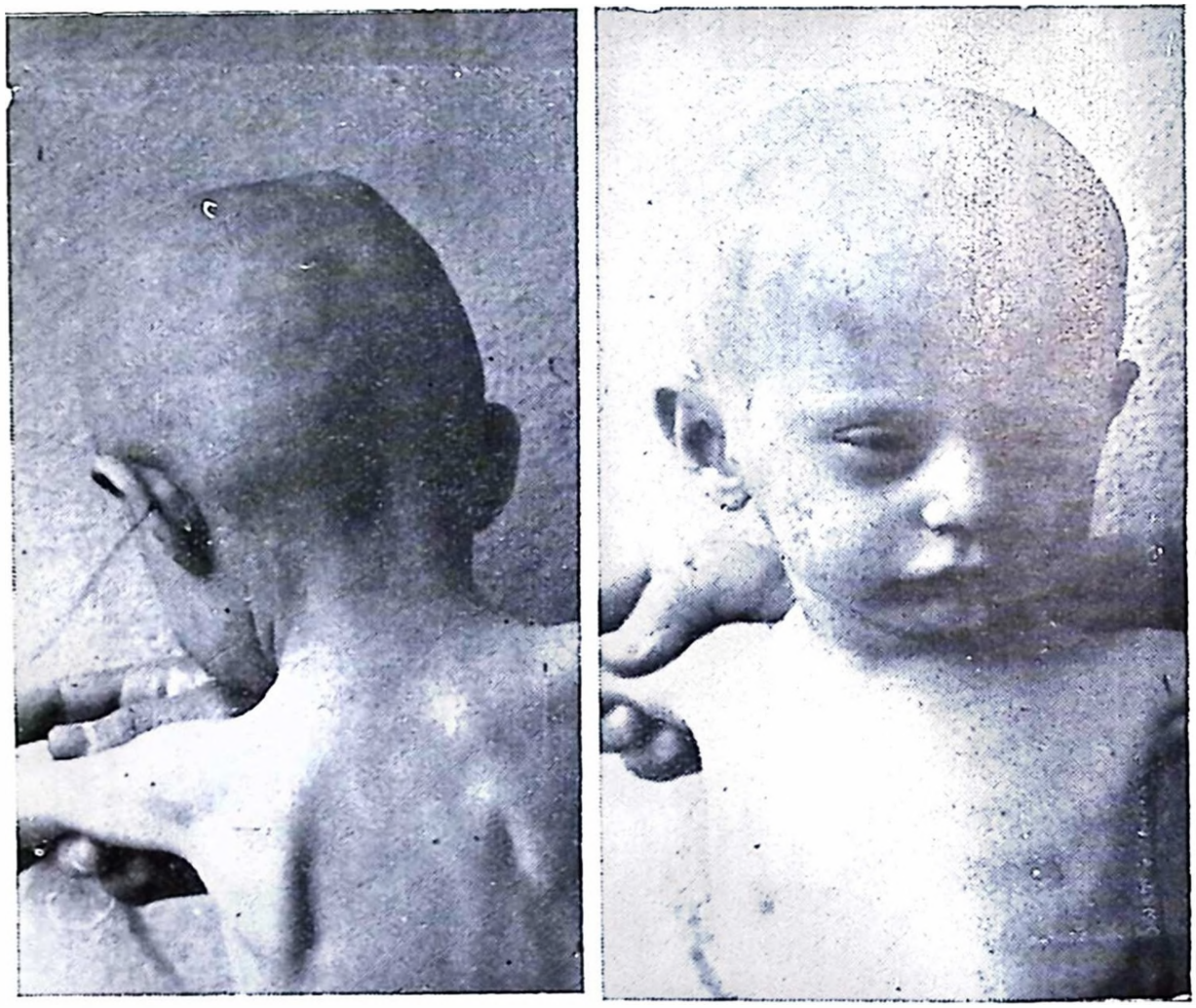




Figures 3. and 4. These photographs show the paronychia of the nails of the hands and feet as well as the erythema and scaling of the tissues around the nails.

in loose flaky scaling. The diarrhea and dehydration responded well to therapy and as she improved in this respect the skin lesions regressed until, within about one week, they were as severe as formerly. Because of the spontaneous improvement, therapy was deferred until her condition was stable.

After approximately two weeks in the hospital she was started on Mysteclin, which was replaced by Mycostatin* when it was



Figures 5 and 6. These views show the improvement in appearance of the lesions of the face, occiput and neck after approximately two weeks of treatment with Diodoquin.

available two or three days later, with each of which she was given three daily doses providing 750,000 units of nystatin. In addition, supportive therapy with emphasis on providing an adequate diet was continued. No topical therapy, other than keeping the lesions clean with soap and water, was utilized. During this period cultures for *C. albicans* were obtained at frequent intervals from various lesions of the skin, the throat and stools. The results of these examinations

* Mycostatin provided by E. R. Squibb and Sons. Istanbul.

are shown in Fig. 8. By the second week of therapy, *C. albicans* was no longer growing in any of the cultures. Nevertheless, the skin lesions continued unabated, and during this therapy there was one minor flare up of diarrhea which had no effect on the skin lesions.

Figure 7. This photograph shows the improvement in the general appearance af the child after therapy. The new growth of nails on fingers and toes is, unfortunately, not clearly evident.

After 15 days of this therapy with no response it was decided to abandon nystatin and initiate therapy with Diodoquin. She was given 210 mgm. daily in two doses and dietary support was continued. There was definite improvement, evidenced by decreasing erythema of the lesions, especially those of the face, within five days. There was progressive improvement over the next two weeks until the skin lesions had almost completely disappeared, including the psoriasiform lesions, and new normal nail growth was appearing on the fingers and toes. Hair had not yet appeared but there seemed to be new growth of eyelashes. It is interesting to note that a further episode of diarrhea occurred during this therapy also. At the end of the

second week on Diodoquin *C. albicans* had not reappeared on the skin or stool cultures, but a few colonies grew out on the throat cultures.

She was discharged on the 52nd hospital day, to continue taking Diodoquin at home. A diagrammatic representation of her hospital course is presented in Fig. 8.

Discussion

Because the role of *C. albicans* remains unclear and because, in surveying the literature available to us, we could find no reference to any attempts to determine the therapeutic effectiveness of nystatin, a drug whose effectiveness against *C. albicans* is well established, we felt that a therapeutic trial was indicated. As indicated in the case report, we found nystatin quite effective against the *C. albicans*, both externally and internally, in this child, but that this had no effect on the cutaneous manifestations of the primary disease process. The literature on the subject [2,3] indicates that a response may be expected within a few days after initiation of therapy and this was borne out by our own subsequent experience with Diodoquin. With this in mind we felt that a two week trial was adequate.

The response to Diodoquin was prompt and satisfactory, as was expected. The dosage we utilized was that used by Dillaha [2] and, in our case, was determined by the size of the tablets available to us. The mechanism of action of this drug eludes us still. This patient, as far as we could determine, was free of *C. albicans* before therapy with Diodoquin was initiated, leading us to believe that its mode of action must be sought elsewhere. Dr. Muvaffak Akman, Chief of the Microbiology Laboratory of the Research Institute of Child Health, carried out sensitivity studies, it should be noted, and found that Diodoquin had no inhibitory effect whatsoever on the growth of *C. albicans* obtained from this patient.

Summary

A brief discussion of acrodermatitis enteropathica has been presented with a case report of an infant with typical findings of this disease who was recently admitted to the Hacettepe Children's Hospital. This is the first recorded instance of the occurrence of this disease in Turkey. The child was subjected to a therapeutic trial with nystatin in the hope of obtaining additional information concerning the role of *C. albicans* in this interesting disease. Nystatin was found to be thoroughly effective in eliminating *C. albicans*, but

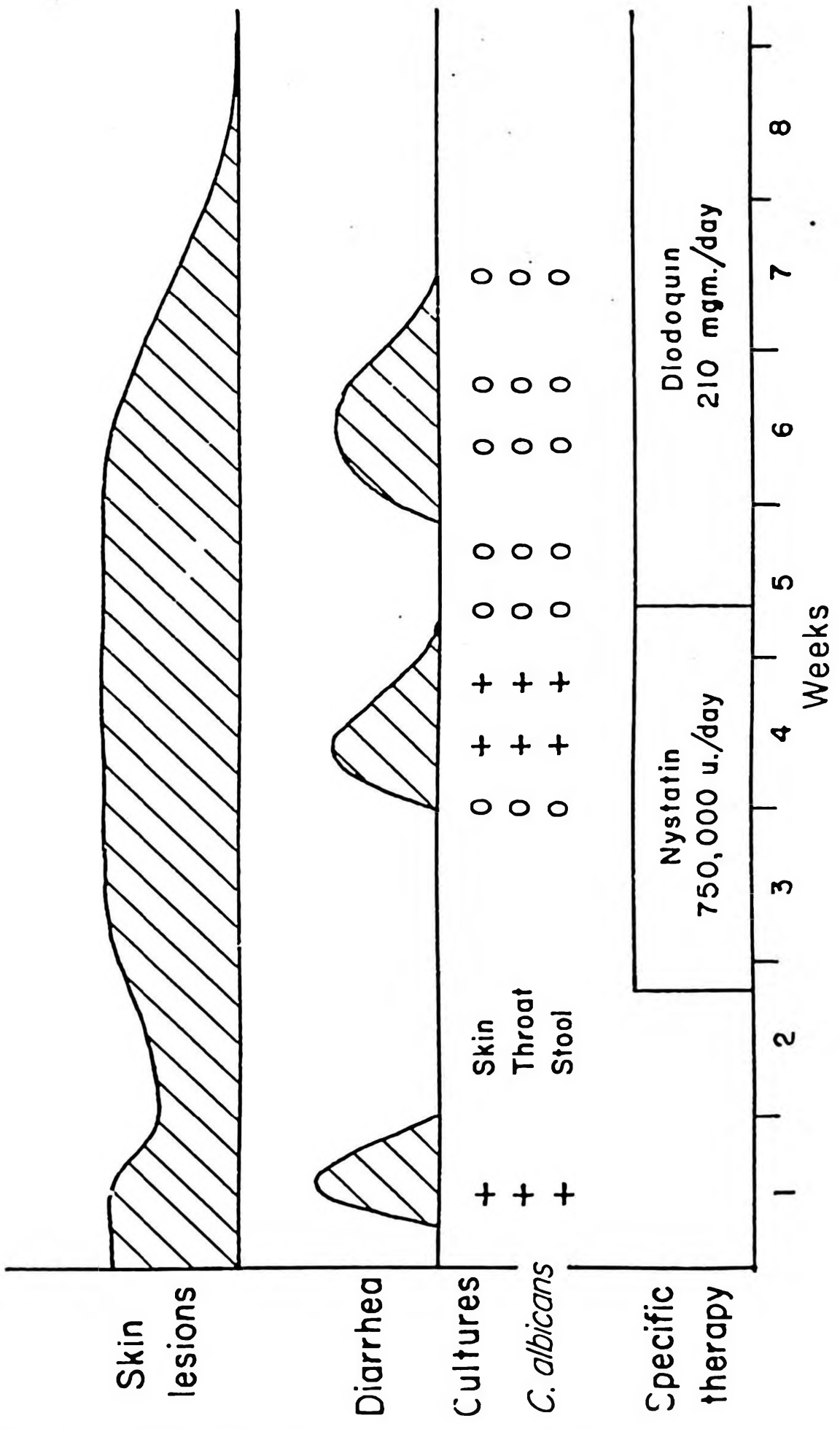


Figure 8. Diagrammatic representation of the hospital course of the patient.

this had no effect on the primary skin lesions. Subsequent therapy with Diodoquin confirmed previous reports of its effectiveness in the management of acrodermatitis enteropathica.

REFERENCES

1. Danbolt, N. and Closs, K.: Quoted by Dillaha [2].
2. Dillaha, C., Lorincz, A., and Aavik, O.: Acrodermatitis enteropathica, J. A. M. A., **152**: 509, 1953.
3. Vedder, J.: Acrodermatitis enteropathica (Danbolt-Closs) in five siblings, J. Pediat., **48**: 212, 1956.
4. Leider, M.: Practical Pediatric Dermatology, Saint Louis, 1956, The C. V. Mosby Company.
5. Sutton, R.: Diseases of the Skin , Saint Louis, 1956, The C. V. Mosby Company, p. 844.
6. Allen, A.: The Skin, Saint Louis, 1954, The C. V. Mosby Company, p. 622.
7. Gellis, S.: Year Book of Pediatrics, 1956-1957 Series, Chicago, The Yearbook Publishers, 1956, p. 378.
8. Ferguson, E. and Rothman, S.: Fungus infections of the skin, Ped. Clin. N. Amer., August 1956.
9. Brandt, T.: Quoted by Dillaha [2] and Vedder [3].
10. Goodman, L. and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1956, p. 1218.
11. Bloom, D.: Quoted by Vedder [3].