

## Chemotherapeutic Trials in Leprosy

### 4. Dapsone (DDS) in Low Dosage in the Treatment of Lepromatous Leprosy A Demonstration Pilot Study<sup>1</sup>

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Although controlled studies are essential to obtain an exact comparison of different treatments, such trials, particularly in leprosy, are complicated, difficult and lengthy, and so are justified only for the most promising of new drugs and drug regimens. It is no longer practical to investigate on a large scale any and every drug that unconvincing clinical evidence suggests may be active in clinical disease. Fortunately, with the discovery of the mouse foot pad test, it is now possible to screen new drugs first in experimental animals (7, 11). In The Research Unit at Sungei Buloh a series of controlled studies have been made on the treatment of leprosy (14, 15), and during these it has become increasingly obvious that if a patient is being successfully treated he will respond bacteriologically and histologically in a predictable manner. These responses will, moreover, occur early in the course of treatment, and we have therefore attempted to develop a form of pilot trial in which, through study of only a few patients for a relatively short period, a definite decision can be made quickly as to the activity of a drug. Feeling our way with a study of the riminophenazine derivative B.663 in lepro-

matous leprosy (5), we evolved a methodology that confirmed our ideas about the practicability of a pilot type trial.

There is now overwhelming experimental evidence that irregularly stained leprosy bacilli are dead and that the majority of solid staining bacilli are alive (8, 12). It was our considered opinion, therefore, that this feature would provide the most sensitive indirect method to determine the rate at which a drug kills leprosy bacilli, and that it could be used, therefore, to assess therapy in patients with lepromatous leprosy who had not received previous treatment. The importance and value of the morphologic index (MI), i.e., the percentage of solidly staining acid-fast bacilli determined from routinely stained skin smears, became increasingly clear, since without exception all cases showed a significant fall, usually to 5 or less, within a period of six months (5, 14, 15, 16). We considered, therefore, that a pilot trial of a new drug or drug regimen could be based primarily on an assessment of the MI. Although, to comply with conventional practice, the bacteriologic index (BI) was recorded, such a relatively inaccurate assessment could not be expected to show any significant change within a period of six months. It has also been demonstrated (14, 15) that the biopsy index usually falls steadily in patients receiving active treatment, particularly when biopsies are taken from areas close to one another in fairly large patches of the disease. We conceived, therefore, that an ideal pilot trial, while paying due attention to the progress of the patient clinically, should in the main be devoted to studying

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the progress of the bacterial and histologic (biopsy index) responses. This paper reports such a trial.

The history of the use of DDS in the treatment of leprosy is truly remarkable. DDS was introduced following the first flush of success with the disubstituted derivative Promin. Yet it would almost certainly have been discarded because of its very severe toxicity at the doses then given had it not been for Lowe's heroic determination to retest DDS at considerably lower doses, which proved to be therapeutically active without toxicity. From his work (<sup>4</sup>) there evolved the somewhat empirically chosen dose of 600 mgm./week, given either orally daily for six days a week at 100 mgm., or given twice weekly by injection of 300 mgm. Despite the acceptance of this as the standard dose throughout the world, for some years, it has been suspected more recently that even this dose is unnecessarily high and that the more intermittent therapy might be as effective. Some workers (<sup>2, 3, 6</sup>) have indicated that 100 mgm. of DDS given orally twice weekly is as effective therapeutically as the standard dose, and they have also suggested that the incidence of erythema nodosum leprosum (ENL) was less at this lower dose. We consider it of the greatest theoretic and practical importance that trials be undertaken to determine precisely the minimum therapeutic dose, and the range of intermittency, for DDS in the treatment of leprosy. Our own work in this field is based on a trial, still in progress, to determine the therapeutic activity of 50 mgm. DDS twice weekly by mouth in at least 20 carefully selected and previously untreated patients with lepromatous disease. This gave us an ideal opportunity to inaugurate a pilot trial of the nature described above on the first six patients, in order to demonstrate that such a trial could produce convincing evidence of the therapeutic activity of this particular regimen.

#### METHOD OF STUDY

In the selection of cases for this trial we have followed our own recommenda-

tions based on the experience gained in an earlier pilot trial (<sup>5</sup>), and we limited the intake to patients who were fully lepromatous, i.e., those patients whose histology showed no features of borderline condition (<sup>10</sup>), and no cases were admitted to the trial whose MI was less than 25. The investigations performed and the methods of assessing progress were based on previously used protocols and, in particular, on that used in a pilot trial of B.663. In order to avoid any form of bias we maintained our practice of using independent assessors for the clinical, histologic and bacteriologic assessments. The full details of the protocol used are set out in the appendix to this paper and we believe that this can be applied to a pilot trial of any therapy in leprosy.

The treatment was in all cases one 50 mgm. tablet of DDS given by mouth twice weekly. Because this trial used such low doses of sulfone we decided to determine the DDS blood levels of the patients in order to provide basic data and also as a specific and sensitive method for detecting whether any patients within the trial were taking more than the prescribed dose. Free DDS blood levels, determined by the method of Bratton and Marshall (<sup>1</sup>), were undertaken on all patients at various intervals, two samples being taken at each time, one immediately preceding and the other six hours after the 50 mgm. dose of DDS.

#### CASE HISTORIES

Case I. (No. 15196) Malay male, age 24. Two years prior to his admission to hospital he noticed a white raised patch on the right cheek, with loss of sensation, and 18 months after this many small nodules began to appear on the face and arms. When first seen at the Settlement he had a heavy lepromatous infiltration, which consisted almost entirely of small confluent nodules. This was most severe on the nose and chin. The ears were somewhat pendulous and there was a thickened auricular nerve on the right side. The lepromin (Mitsuda) test was negative

(3 mm.). The smears on admission gave an average BI of 4.5 and MI of 42. Two biopsies of skin, taken respectively from the left back and right arm, showed typical lepromatous leprosy (LL) and the biopsy index was 2.0. The tuberculin test gave a reading of 30 mm. to 1 TU.

**Case 2.** (No. 15197) Chinese male, age 37. This patient developed a reddish patch on the left leg two years prior to admission, and later a large number of small nodules appeared all over the body. Just before he came to hospital many of the lesions suddenly became red and swollen, and on admission he was suffering from a mild lepra reaction in addition to severe nodular lepromatous leprosy. The whole of the face was covered with large nodules, and on the body, arms, and legs there was very little clear space between the individual nodules, many of which were 1 or 2 cm. in diameter. Both hands were edematous, and anesthesia was present on the left foot, although it was impossible to palpate any hard or enlarged peripheral nerves. The lepromin (Mitsuda) test was negative (0 mm.). The smears on admission gave an average BI of 4.1 and MI of 37. The biopsies of skin taken from the right back and left elbow showed active lepromatous leprosy (LL), but no sign of any lepra reaction, and the biopsy index was 3.85. The tuberculin test was negative to 1 and 20 TU, but at the completion of four and one-half months of treatment there was a 3 mm. reaction to 1 TU.

**Case 3.** (No. 15210) Chinese male, age 20. This patient was admitted to hospital with a six month history of red spots developing on the abdomen, face, and arms. Three weeks before he came in he had developed a small patch of numbness on the sole of the left foot, which caused him to suspect that he had leprosy and to consult his own doctor. On examination the face, chest, body, and limbs showed diffuse infiltration, with some small nodules on the posterior aspect of both arms and many papules and nodules on the face. Both ulnar nerves and the right great auricular nerve were thickened, but in spite of the history there was no detectable sensory loss. The lepromin (Mitsuda) test was negative (0 mm.). Smears on admission

gave an average BI of 4.1 and MI of 31. The biopsies of skin taken from the right scapula and right shoulder showed slightly active lepromatous leprosy (LL) with a biopsy index of 2.25. The tuberculin tests to 1 and 20 TU on entry and at the completion of the trial were negative.

**Case 4.** (No. 15218) Chinese male, age 45. Twelve years before admission the patient had a patch of numbness on the left foot and developed a foot drop. He was treated elsewhere for a few months with sulfone at that time and stopped treatment about 11 years before admission to our Settlement. Three months prior to his admission a number of rather red shiny patches appeared on the face, arms, and legs, which were somewhat anesthetic. On examination, the patient had a mild diffuse lepromatous leprosy of the whole of the body and face. The great auricular nerves, the ulnar nerves, and the lateral popliteals were thickened on both sides, and there was some weakness and wasting of the left leg, which also showed anesthesia peripherally. The lepromin (Mitsuda) test was negative (0 mm.). Smears on his admission gave an average BI of 3.7 and MI of 26. Both biopsies of skin showed active lepromatous leprosy (LL) and a biopsy index of 1.0. Tuberculin tests to 1 and 20 TU on entry and at the completion of the trial were negative.

**Case 5.** (No. 15245) Chinese male, age 31. An anesthetic patch about six inches in diameter appeared on the right thigh about six years prior to admission. A few weeks before coming to hospital he noticed a number of nodules appearing on the feet and ankles. On examination he showed diffuse infiltration of the whole of the body, with very few nodules on the ears and around the ankles. The peripheral nerves were not significantly enlarged and there was no detectable sensory loss, except for the anesthetic area that had originally appeared on the thigh. The lepromin (Mitsuda) test was negative (0 mm.). On admission the skin smears gave an average BI of 4.0 and MI of 25. The biopsies of skin, taken from both sides of the lower back, showed active lepromatous leprosy (LL), and the biopsy index was 1.0. The tuber-

culin tests to 1 and 20 TU on entry and completion of the trial were negative.

**Case 6.** (No. 15250) Chinese male, age 31. This patient had a 12 year history of an anesthetic patch appearing on the right knee and outer side of the calf, and gradually of other patches of diminished sensation appearing over the body and limbs. One year before he came to hospital a sudden crop of red spots appeared, and when he was first seen he had a leonine face with raised, rather brownish lepromatous nodules and plaques, particularly on the face, abdominal wall, and right flank. Clinically he showed a very mild lepra reaction. Both ulnar nerves were thickened and there was some clawing and wasting of both hands. He showed also a patchy anesthesia in most parts of the body, which seemed to be associated with the skin infiltration rather than nerve trunk involvement. On admission the lepromin (Mitsuda) test was negative (0 mm.). The smears from both ear lobes were negative, but all other lesions were highly positive, giving an average BI of 2.8 and MI of 41. Biopsies of skin taken from the right flank and the left abdomen showed active lepromatous leprosy (LL) with a biopsy index of 2.5. The tuberculin test gave a reading of 13 mm. to 1 TU.

## RESULTS

A number of subsidiary assessments and tests were carried out throughout the trial as laid down in the protocol. They included

examination of the urine and sputum, blood counts, x-ray examinations of the chest, and lepromin and tuberculin tests, as well as the weight of the patients. None of these showed important changes and they will not be considered any further in this paper.

The main assessments were based on clinical, bacteriologic and histologic progress, and unless otherwise stated these were confined to the first four and one-half months of treatment.

**Clinical.** The Independent Assessor reported that each of the six cases showed some improvement; four were marked as showing slight improvement and the other two were placed on the border between slight and moderate. In other words the clinical progress of the patients was as expected after a short period of treatment with standard doses of DDS, and there was no indication that the lower dosage of DDS was less effective. None of the patients developed ENL during this period.

**Bacteriologic.** The findings are summarized in Table 1 and the details of the MI for six months are shown in Figure 1. In all patients there was a dramatic fall in the MI at the completion of four and one-half months of treatment, and there was no further significant change six weeks later. These results duplicate those of our previous studies, and it is believed that on this evidence alone it can be stated with some certainty that the treatment under investigation has been satisfactory as far as antibacterial activity is concerned. The results of the BI, which are also given,

TABLE 1. Bacteriologic and histologic response of 6 patients treated for 4½ months with DDS (50 mgm. twice weekly).

Case No.	Period of treatment				Percentage fall in biopsy index
	At start	After 4½ months	At start	After 4½ months	
	Bacterial index (BI)		Morphologic index (MI)		
15196	4.5	5.0	42	1	10
15197	4.1	5.0	37	0	33
15210	4.1	4.3	31	1	38
15218	3.7	4.1	26	1	33
15245	4.0	4.3	25	0.5	55
15250	2.8	2.7	41	1	10
Average	3.9	4.2	34	0.75	30

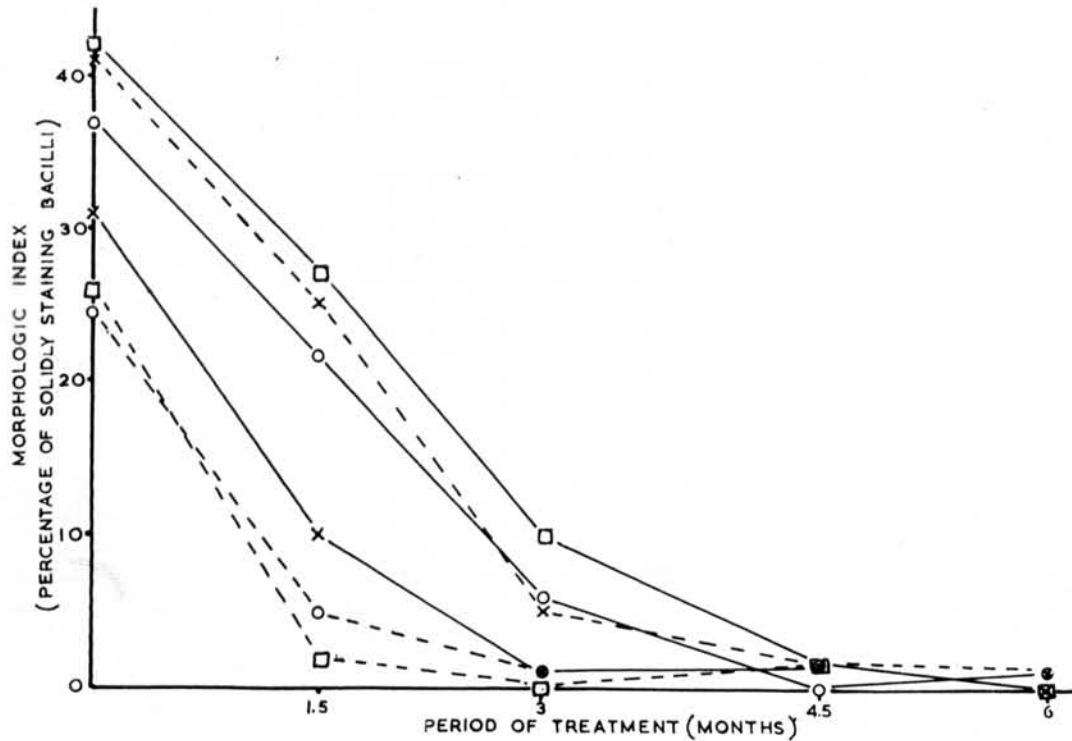


FIG. 1. The effect of treatment with DDS (50 mgm. twice weekly) for 6 months on the morphologic index (MI) in 6 previously untreated lepromatous patients. Case 1, □—□; case 2, O—O; case 3, X—X; case 4, □·····□; case 5, O·····O; case 6, X·····X.

show that in all cases except one there was no fall; indeed most cases showed a rise of as much as 20 per cent. Over such a short period these results are not unexpected from a technic that has no claims to scientific accuracy.

**Histologic.** Table 1 shows considerable variation in the biopsy indices, with improvement ranging between 10 and 55 per cent (average 30 per cent). As this index was designed primarily to assess the progress of a group, individual results are not reliable unless there are at least two six-monthly periods of observation (<sup>9</sup>). The mean fall of 30 per cent is comparable with that expected in patients receiving standard DDS therapy.

**DDS blood levels.** The mean blood levels of DDS immediately before and six hours after a dose of DDS were 0.09  $\mu$ gm./ml. (range 0.0–0.3) and 0.75  $\mu$ gm./ml. (range 0.2–1.6), respectively, on samples of blood taken from the patients at inter-

vals throughout the trial period. This dosage schedule gives no evidence of a build-up in the blood levels during treatment, and, moreover, the blood levels on all the patients throughout the trial were consistent and significantly lower than those found in patients receiving the standard dose of 600 mgm. of DDS per week. Therefore, there was no evidence that any of these patients were taking significantly higher doses of DDS than those laid down in the protocol.

## DISCUSSION

Experience gained from a series of controlled studies has taught us that specially selected patients will respond in a predictable manner to an effective anti-leprosy drug, and that this response will occur early in the course of treatment. We have attempted, therefore, to develop a

form of pilot trial that will demonstrate antileprosy activity, using only a few patients and a relatively short period of observation. We believe that the selection of patients for such a pilot trial is of paramount importance. The intake must be restricted to a group with comparable prognostic expectations; i.e., it should be confined to previously untreated patients with pure lepromatous disease (confirmed both clinically and histologically) whose mean MI is not less than 25. This ensures as far as possible the exclusion of patients whose disease is inactive or partly treated, and also avoids the pitfalls of including the more labile-type cases, i.e., those with borderline features. It is reasonable to assume that if there is a significant fall of the MI in these selected patients within a period of four and one-half to six months, the bacteria have been killed by the drug under test.

We believe that our results show that a pilot trial is a valid method of investigation. Although clinical, histologic and bacteriologic (BI) examinations were made, both before and during treatment, particular weight was given to the MI. This showed the same rate of fall as in two recent large-scale trials<sup>(14, 15)</sup>, and we consider that at the end of only four and one-half months of treatment we had excellent evidence that small doses of DDS were fully effective in the treatment of lepromatous leprosy. Although the trial was extended to six months, our original suggestion that a pilot trial should last four and one-half months, seems justified. This trial incorporated the early months of the first patients in a more prolonged study planned to investigate whether low dosage of DDS significantly diminishes the incidence and severity of erythema nodosum leprosum. The larger trial has a minimum intake of 20 cases of lepromatous leprosy which will be observed for at least a year. It is hoped that the results in the first six cases will be confirmed by the larger number, and so prove that a small pilot trial based on the MI is of great value for the clinical screening of a new form of treatment.

The preliminary results show clearly that 50 mgm. of DDS twice weekly for six months is no less effective than the stand-

ard dose of 600 mgm. per week. These results agree with other studies<sup>(2, 3, 6)</sup>, which indicate that 200 mgm. of DDS weekly is as effective as the standard dose. Although the results of the larger trial must be awaited, it is already apparent from our studies that the inhibitory DDS blood level is significantly lower than has heretofore been realized. As there is increasing evidence from studies on DDS in the mouse foot pad infection that the multiplication of *Mycobacterium leprae* can be inhibited by very low doses of DDS as measured in the blood<sup>(7, 13)</sup>, we consider it of the greatest theoretic and practical importance that trials be undertaken to determine the minimum therapeutic dose, and the range of intermittency, for DDS in the treatment of leprosy. Trials of this type in man, together with the foot pad technic, provide an opportunity, for the first time, of putting DDS therapy on a scientific, rather than an empiric basis. We believe the pilot trial as described in this paper will be of the greatest aid in the rapid determination of the therapeutic activity of lower doses or different regimens of DDS in man.

## SUMMARY

A method of studying chemotherapy in leprosy has been evolved, which, by use of a pilot trial, enables decisions to be made as to the value of a drug in only six patients and over a period of less than six months. In the demonstration trial reported here 50 mgm. of DDS twice weekly by mouth was shown to produce as satisfactory bacterial, histologic and clinical improvement as the higher doses that are usually used.

## RESUMEN

Se ha desarrollado un método para estudiar la quimioterapia en lepra, el cual, usando un ensayo piloto, permite hacer decisiones relativas al valor de la droga en solo seis pacientes y en un período de tiempo inferior a seis meses. En el ensayo de demostración del que

se habla 50 mgm. de DDS dos veces por semana dados por vía oral demostraron producir mejoría tan satisfactorias bacteriológica, histológica y clinicamente como las conseguidas con las dosis mas altas que se emplean ordinariamente.

### RÉSUMÉ

On a mis au point méthode permettant d'étudier la chimiothérapie dans la lépre, qui, grâce à l'emploi d'une étude pilote, permet de poser un jugement sur la valeur d'un médicament chez seulement six malades et après une période de moins de six mois. Dans l'expérience de démonstration relatée ici, on a montré que 50 mgm. de DDS deux fois par semaine, administrés par voie orale, produisaient une amélioration bactériologique, histo-

logique et clinique aussi satisfaisante que les doses plus élevées qui sont généralement utilisées.

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## APPENDIX

### Recommended Protocol for a Pilot Trial

1. **Objective:** To assess the therapeutic activity of a drug in patients with lepromatous leprosy.
2. **Type of patient to be admitted to the trial.**
  - (i) Adults, 15 years and over in age.
  - (ii) They must have clinically lepromatous leprosy, with a morphologic index (MI) of not less than 25 per cent.
  - (iii) Histopathologically, they must be pure lepromatous (LL type) with a biopsy index of 0.5 or more for each initial biopsy<sup>(9, 10)</sup>.
  - (iv) They must have no other significant organic disease.
  - (v) They must have had no previous scientific treatment for leprosy.
3. **Initiation of trial:**

All patients should be hospitalized throughout the trial.  
Six patients should be the minimum intake.
4. **Preliminary investigations by Doctor in charge of the trial:**
  - A. General**
    - (i) Complete clinical examination.
    - (ii) Complete urine examination including microscopy.
    - (iii) Hemoglobin, white blood and differential count.
    - (iv) X-ray of chest.
    - (v) Examination of sputum, if any.
    - (vi) Weight of patient.
  - B. Leprosy.**
    - (i) Clinical examination of the leprosy condition,

- (ii) Smears from 6 sites, including both ear lobes, recording the bacteriologic index (BI) and MI.
- (iii) Two biopsies.
- (iv) Color photographs.
- (v) Lepromin (Mitsuda type) skin test.
- (vi) Tuberculin skin test. Mantoux technic, 1 TU to be used (a second dose of 20 TU being given, should the first one give a negative result, i.e., a diameter of induration of less than 5 mm.).

**5. Initial examination by the Independent Assessor:**

Clinical examination of the patients' leprosy condition with detailed notes and charting of lesions on record sheets supplied. Color photographs (Para. 4B (iv)) will also be submitted to the Assessor.

**6. Observations by Doctor throughout treatment:**

**A. General**

- (i) Hemoglobin, white blood and differential counts—monthly.
- (ii) Urine—Albumin and urobilinogen—monthly.

**B. Leprosy.**

Smears from 6 sites recording the the BI and MI every 1½ months for 4½ months.

**7. After 4½ months' treatment:**

**A. Investigation by Doctor:**

- (a) *General:*
  - (i) Complete clinical examination.
  - (ii) Complete urine examination including microscopy.
  - (iii) Weight.
- (b) *Leprosy:*
  - (i) Smears—as in Para. 4B (ii).
  - (ii) Two biopsies.
  - (iii) Color photographs. Tuberculin test. Repeat as per Para. 4B(vi). Do not retest with a dose that produced a reaction of 30 mm. or more previously.

**B. Assessment by Independent Observer.**

- (i) Clinical examination of the patient's leprosy condition with detailed notes and charting of lesions. When this has been done, photographs of the patient will be made available to the Assessor. Biopsy reports and smears will *not* be made available to the Assessor.
- (ii) The Assessor will then pass an opinion as to the change, if any, in the patient's condition, as follows:

*No change.*

Self explanatory.

*Improvement.*

1. Slight. Some diminution in size of lesions with or without some return to normal pigmentation.
2. Moderate. Between slight and marked.
3. Marked. Marked diminution in the size of the lesions and possible disappearance of some.

*Deterioration.*

1. Slight. Some increase in size of the lesions.
2. Moderate. Between slight and marked.
3. Marked. Marked extension of lesions with or without the appearance of new lesions.

If the Assessor believes that the above classification is not suitable in an individual case, he may indicate that the patient's condition has changed to any intermediate position, i.e., "between slight and moderate" improvement or "between no change and slight deterioration," etc.

**8. Reactions**

The Assessor is concerned chiefly with the underlying leprosy condition, but he should note at every assessment of every patient the presence or absence of a reaction and as far as possible should specify the type. As the signs of a reaction may be considerably affected



by steroid therapy, the Doctor in charge of the trial will inform the assessor after the latter has completed his clinical examination with notes if the patient is receiving steroid therapy for reaction and the current dose being given.

The Doctor in charge should also record the type and severity of reactions throughout the study. For ease of analysis these should be recorded as follows:

#### *Lepra reactions*

- + doubtful reaction.
- + definite mild reaction, usually responding to standard treatment.
- ++ moderately severe reaction, usually responding poorly to standard therapy, and often

requiring corticosteroids for a short period.

#### *ENL reactions*

- + mild, causing little discomfort and responding to standard therapy.
- ++ moderate, usually persistent, and not easily controlled by standard therapy; requiring occasional steroids or ACTH.
- +++ severe, persistent, causing very considerable discomfort, requiring regular steroids and/or ACTH.
- ++++ very severe, usually necrotic, requiring high doses of steroids and/or ACTH for long periods.

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