

## ERYTHEMA NODOSUM IN LEPROSY

by

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Erythema nodosum has long held a spotlight in dermatology as an example of a condition which shows amazingly little histologic alteration of the tissues, compared with the violent inflammatory appearance of the lesions themselves. Most present day opinions recognize the complex as a manifestation of general hypersensitivity, the local changes resulting from some injury or alteration in the peripheral subcutaneous blood vessels. Erythema nodosum is well known as a complication of various subacute and chronic infectious processes, from typhoid fever to tuberculosis. Probably it is nowhere more brilliantly demonstrated than in leprosy.

It is the purpose of this paper to record observations concerning the occurrence and management of erythema nodosum as seen in the course of leprosy at Carville. Medical texts do not often suggest leprosy as one of the many conditions in which erythema nodosum may be found and the medical literature contains relatively few articles discussing the occurrence, significance, or treatment of erythema nodosum in leprosy.

The literature of leprosy commonly confuses erythema nodosum with the *acute lepra reaction* by referring to both processes as "acute reactions." In our experience there is a sharp distinction to be drawn between the "acute reaction" which is erythema nodosum and the genuine acute *lepra* reaction, which latter is signalized by increased numbers of organisms throughout all the leprous lesions of the body, together with rapid and inflammatory increase in size and numbers thereof. The two conditions are altogether different in character; they are never concurrent, they carry altogether different prognoses, and they are readily distinguishable clinically.

The line of demarcation which exists between the acute *lepra* reaction and erythema nodosum may be pictured by a brief summary of differentiating characteristics:

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<i>Acute lepra reaction</i>	<i>Erythema nodosum</i>
1. Onset abrupt	1. Onset variable
2. Course steady for weeks or months	2. Showers of evanescent lesions
3. Bacilli increasingly abundant	3. Bacilli rarely present
4. Lesions include: <ul style="list-style-type: none"> <li>a. Recrudescence of old lesions</li> <li>b. Eruption of new lesions</li> </ul>	4. Lesions discrete and not related to the areas of leprous activity
5. Lesions not painful on pressure	5. Lesions usually painful on pressure
6. Prolonged fever for weeks or months	6. Some afebrile; others have fever intermittently for weeks or months
7. Wasting and loss of weight common	7. Weight and strength maintained
8. Rare during sulfone treatment	8. Common with sulfone treatment
9. Leprous histopathology	9. Vascular changes with fibrinoid swelling of collagen
10. Residual contractures, paresis, etc. with leprous state worse	10. Skin elasticity may be lost after repeated attacks but leprous state is the same or improving

*Erythema nodosum* occurs among Carville patients as an acute, subacute, or chronic skin eruption, with or without fever, which is characterized by showers of reddened nodules found most commonly on the extensor surfaces of the extremities, on the face, and occasionally on the trunk. The nodules are usually tender to touch. Some patients experience a sudden onset. Nodules may cover much of the body within a few hours and the temperature may rise to 103° or 104° F. In spite of anorexia and malaise during the diurnal temperature rise the patient's general condition remains good. Such a condition may last for several weeks with occasional days when the fever and eruption seem about to subside only to be followed by an outpouring of new lesions and a fresh rise in temperature. Uncontrolled cases subside gradually and the temperature falls by lysis. Other patients in whom the course is less acute may continue to show a few scattered evanescent nodules much of the time, with only a minimum of fever or discomfort.

The lesions of *erythema nodosum* usually remain discrete and

may vary from 0.5 to 5 cm. in diameter. They seldom extend peripherally or coalesce. Within the past twelve months only two cases have been known to progress to pustulation; in both instances the patients had been absent from the leprosarium for several weeks, without medical supervision, and returned with massive pustules of the arms and legs resulting from broken-down lesions of erythema nodosum.

Multiple attacks of erythema nodosum appear with great frequency in some patients; others have experienced only two or three attacks in many years. The first few attacks usually subside and leave the skin relatively normal in color and consistency. Repeated and prolonged episodes with fever often leave residual changes, such as dark spots of purple, brown, or blackish hue. Loss of elasticity gives the affected skin a glossy sheen and a board-like consistency. The occurrence of lesions along nerves, such as the ulnar, occasionally gives rise to an intense neuritis for a short time.

The histopathologic picture of erythema nodosum is basically due to vascular changes in the smaller subcutaneous vessels and their branches in the corium. The visible damage to these vessels is slight. The vessel walls may appear swollen, with some suggestion of endothelial proliferation. There is often edema about the vessels, so that they are a little separated from the neighboring tissues. Inflammatory cells may infiltrate along a few of the vessels, yet their number is small, and it is not certain whether they appear in relation to injury to the vessels or are merely accumulations in perivascular lymphatics draining the skin. The most striking change in the dermis is the edema of the corium. Even though leprous infiltrations may be accidentally caught in the lesions, there seems to be no especial change in them. The connective tissue fibers of the corium appear swollen, stain unevenly, and individual necrotic fibers can often be found. Although the lesion has been likened to the Schwarzman phenomenon (especially in the apparent lack of a *specific* activating factor), the histologic changes are usually rather slight. The tissue extravasations are composed mostly of plasma, and are rarely, if ever, hemorrhagic in character. Indeed the histology of the lesion is more like that of the Arthus phenomenon. Although the whole picture strongly indicates an antigen-antibody immune reaction on a basis of local tissue sensitivity, the mechanism is far from clear.

A review of case records, corroborated by direct questioning of the 396 patients, yields the following data concerning the occurrence of erythema nodosum ("tubercles" in the local vernacular):

History of erythema nodosum	Number	Per cent
Absent	148	37
Present	248	63
Total	396	100

Further analysis of the 248 cases in which erythema nodosum has occurred shows an obvious correlation between the institution of treatment for leprosy and the appearance of erythema nodosum:

Erythema nodosum	Number	Per cent
Before treatment	17	7
After treatment	231	93
Total	248	100

The condition usually occurs within six to twelve months after treatment is started. Although it has been seen in the course of several different regimens of treatment which have been employed in past years it is the consensus of the staff that erythema nodosum has become much more common since the initiation of sulfone therapy.

Still another indication of a correlation between treatment and the occurrence of erythema nodosum is shown by observations of the 42 cases admitted during the current calendar year (in which the maximum period of sulfone treatment would be eight months):

History of erythema nodosum	Number	Per cent
Absent	26	62
Present	16	38
Total	42	100

It appears to be statistically significant that in this group of cases of comparatively brief duration and still more brief period of treatment the incidence of erythema nodosum is distinctly lower.

Ten of the 16 patients with erythema nodosum in this group suffered the first attack only a few months after sulfone treatment had been started. Three of the 16 patients had been originally admitted to the hospital sometime prior to 1947 and had experienced erythema nodosum during such previous admission. A brief case history of one of these patients is of interest:

Case No. 1847 is that of a Mexican male patient, born in 1922. His

first admission was in September 1941 (classified L<sub>1</sub> at that time) when he received promin therapy for eight months before absconding. The first evidence of erythema nodosum was in December 1941. The patient states that the "tubercles and fever" continued at irregular intervals until about 1944 and that during this period his lepromatous nodules remained in abeyance and his face was quite clear. He adds that when the "tubercles" ceased the lepromatous nodules began to grow gradually in size and number until his condition made further treatment essential. He returned as a patient (now L<sub>2</sub>N) in May 1947 with many discrete lepromata of the face, lips, and ears, and superficial ulcers on the face and legs. Three months after promin treatment was resumed the lepromata showed a definite decrease in size, the ulcers healed, and crops of erythema nodosum with fever recurred.

Instances in which clinical and bacteriologic arrest of leprosy has followed closely upon repeated and severe attacks of erythema nodosum have often been striking. Such occurrences may be coincidental; however, when they are considered along with the apparent relation between treatment and the appearance of erythema nodosum it seems highly probable that they offer a definite indication of the resistance of the host.

The management of erythema nodosum at Carville has included a host of remedies during the past years; antipyretics, purgatives, bed rest, calcium salts, penicillin, Fowler's solution, vitamin preparations, benadryl, insulin, and others. All regimens produced some improvement in some cases, but there always remained a number of patients whose antilepromatous treatment was being withheld while they were suffering from prolonged febrile episodes of erythema nodosum.

Germond (1) in 1940 described the successful use of fuadin in the treatment of what he called the "acute lepra reaction." This trivalent antimony compound of pyrocatechin sodium disulfonate

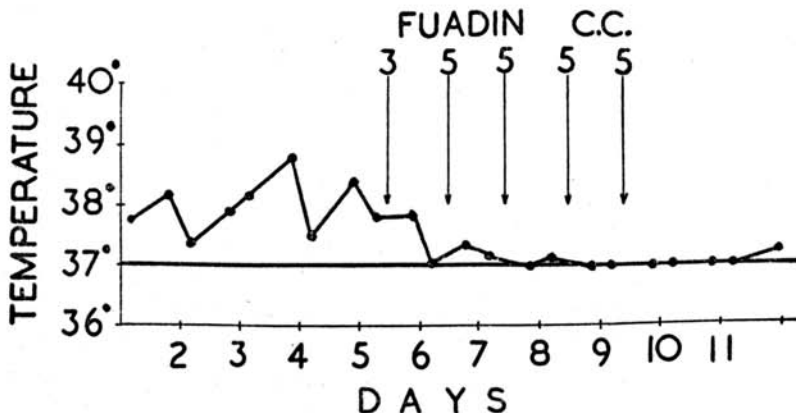


FIG. 2. Case No. 1741. Response to fuadin after fever of several weeks' duration.





FIG. 1. Case No. 1688. Erythema nodosum lesions.

has been used at Carville in the treatment of erythema nodosum since August 1946. The drug is injected intramuscularly and the usual dosage schedule is:

1st day	3 c.c. fuadin (25.5 mg. antimony)
2nd day	5 c.c. fuadin (42.5 mg. antimony)
3rd day	5 c.c. fuadin
4th day	5 c.c. fuadin
5th day	5 c.c. fuadin

A longer series of injections has failed to effect any relief in cases of apparent failure and lesser amounts have appeared to be inadequate in a few instances.

More than 1000 injections of fuadin were given to a total of 140 patients with erythema nodosum between August 1946 and August 1947. Many patients received more than one series of injections when the condition recurred weeks or months later, e.g.:

Series of injections	Patients	Total Injections
1	97	481
2	26	263
3	12	176
4	2	41
5	2	50
6	1	26
Totals	140	1037

In general the improvement noted after fuadin therapy is commensurate with the severity of erythema nodosum. Individuals who have an intense generalized eruption and high fever usually feel and look surprisingly better after the first injection of the drug. The effect on their fever is shown in the accompanying temperature records. Patients who show minor attacks of erythema nodosum with only a scattering of lesions and without fever usually do not show as dramatic a response to fuadin therapy. The use of fuadin does permit the antileprous treatment to continue without interruption in practically all patients.

The clinical results obtained in the treatment of 209 attacks of erythema nodosum in 140 patients are summarized as follows:

Diagnosis	Number of attacks	Relieved*	Improved**	Failure***
Erythema nodosum with fever	123	96 (78%)	19 (15%)	8 (7%)
Erythema nodosum without fever	86	49 (57%)	22 (26%)	15 (17%)

*Definitions:*

- \* Return to pre-erythema nodosum status in 5 days
- \*\* Clinical improvement in 5 days
- \*\*\* No improvement

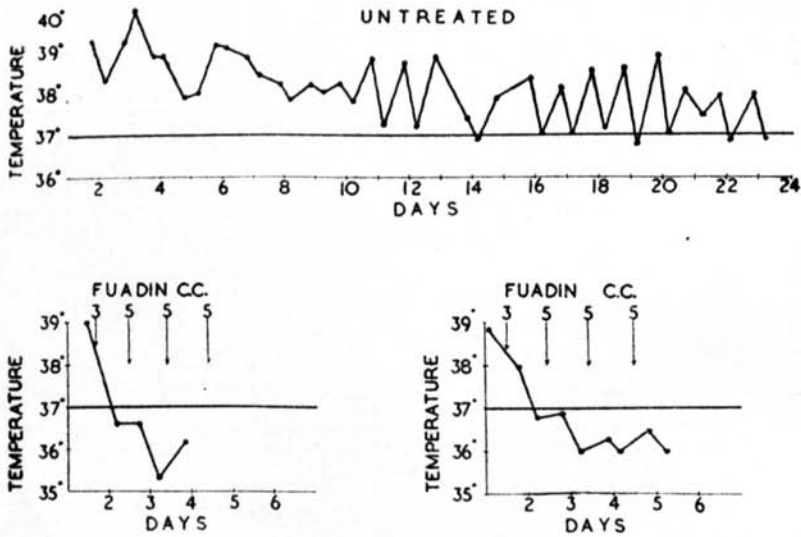


FIG. 3. Case No. 1707. Upper: Record of fever for 23 days prior to use of fuadin for erythema nodosum. Lower left and right: Response of fever to fuadin during subsequent attacks.

The injection of fuadin is not accompanied by any more local pain than is the introduction of other fluids in like amounts. Constitutional symptoms of toxicity attributable to fuadin have not been observed in the doses used. In many cases fuadin and sulfone drugs have been given concurrently.



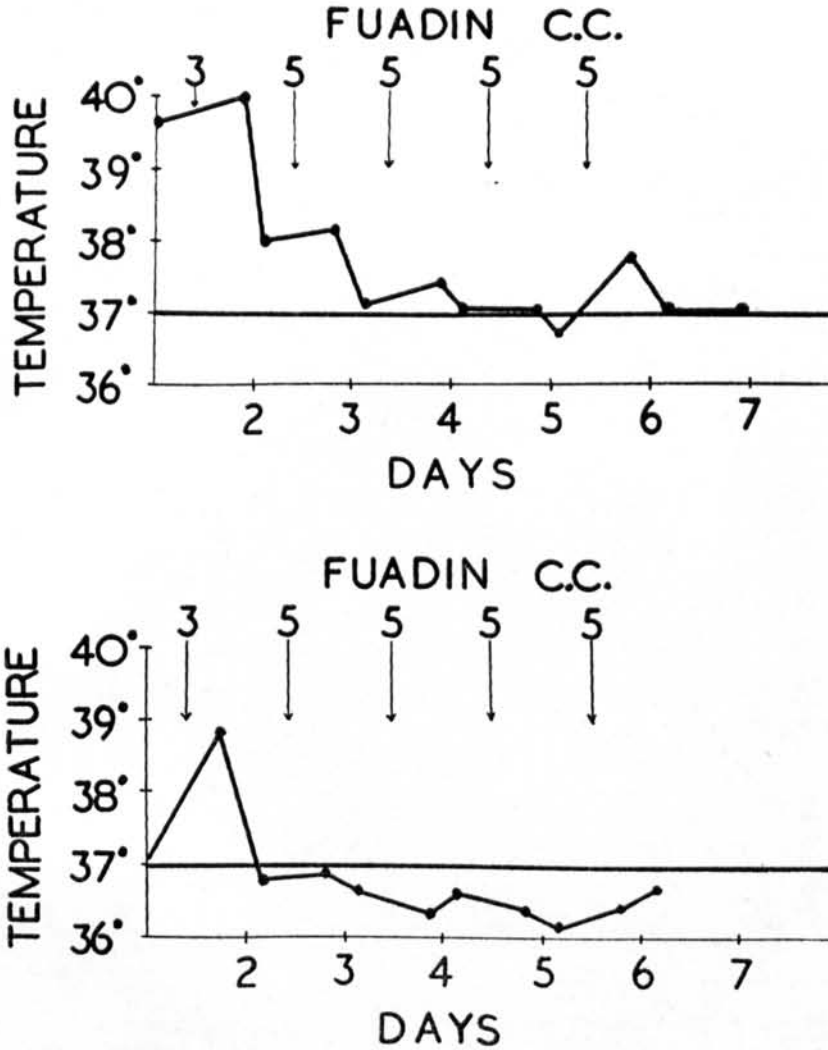


FIG. 4. Upper: Case No. 1729. Response of erythema nodosum fever to fuadin: lesions had progressed to pustulation.

Lower: Case No. 1691. Response to fuadin.

#### SUMMARY

1. Erythema nodosum occurs among a large proportion of the cases of leprosy seen at Carville.

2. A correlation between antileprous treatment and the appearance of erythema nodosum is indicated by the observation that 7 per cent occurs before treatment and 93 per cent after treatment.

3. The suggestion is made that the presence of erythema nodosum indicates an increasing resistance to the disease.

4. An antimony compound (fuadin) has been found to be a satisfactory agent for the control of the fever and discomfort of erythema nodosum and is considered a useful adjunct to the sulfone drugs in the management of leprosy.

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#### REFERENCES

- (1) Germond, R. C. Treatment of lepra reaction and lepromatous ulcers by antimony and arsphenamides. *Internat. J. Leprosy.* 8 (1940) 29.