ERYTHEMA NODOSUM IN LEPROSY*

A STUDY OF THE PATHOGENESIS WITH REFERENCE TO CARBOHYDRATE METABOLISM

by

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Erythema nodosum is generally regarded as a non-specific inflammatory reaction of the skin caused by a variety of agents. The pathological changes usually seen include vascular dilatation, marked edema of the collagen, and small round cell infiltration, which is largely perivascularly arranged in the middle and lower portions of the corium and to a lesser extent in the papillary and subpapillary portions. Epidermal changes are usually absent. Clinically, the lesions are reddish evanescent nodules of variable size and of variable duration. Erythema nodosum is usually described as being associated most commonly with tuberculosis and streptococcal infections (1,2,3,4,5). In addition, there are a number of other conditions which have been mentioned as causing erythema nodosum occasionally, some of which are coccidioidomycosis, drug intoxication, rheumatic fever, ulcerative colitis, upper respiratory infections, arthralgias, inactive syphilis, gonorrhea, herpes zoster, measles, and prostatic abscess (6,7,8,9,10,11,12).

At the National Leprosarium in Carville, Louisiana, there are 372 patients. Among the frankly lepromatous type of cases, 29 per cent have never suffered from erythema nodosum, 46 per cent have suffered some time in the past, while 25 per cent have some lesions at present or have had during the past two months. The percentages among frankly mixed cases are similar, 34 per cent have never shown erythema nodosum, 40 per cent have had it some time in the past, while 26 per cent are suffering at present or within the past two months. Among patients with neural leprosy, the amount of erythema nodosum is considerably smaller, 67 per cent never having had any symptoms of it, 22 per cent having suffered at some time in the past, and only 11 per cent having evidence at present or within the past two months.

Erythema nodosum does not seem to be a manifestation of the

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modern treatment of leprosy with sulfone derivatives, notably diasone and promin (13). Among the patients treated with promin intravenously there were 27 who suffered with erythema nodosum, In 52 per cent the erythema nodosum was improved on promin, while 33 per cent got worse and in 15 per cent there was no change (14,15). In the diasone group 12 patients suffered from erythema nodosum, 50 per cent of these showed improvement in the erythema nodosum on diasone, in 42 per cent it got worse, while 8 per cent were not influenced (16). It would seem therefore that the erythema nodosum seen with leprosy is neither caused nor cured by the treatment.

Leprosy is a disease which can be manifested in many acute ways and in many chronic ways. The present study of changes in the carbohydrate metabolism among patients with leprosy was conducted for the purpose of studying differences between the metabolism of patients with acute lesions and those with only chronic manifestations.

ANALYTICAL METHODS

Approximately 5 cc. of blood was withdrawn by venous puncture after a 14-hour fast, oxalated and used for the Folin-Wu filtrate which was utilized for the blood sugar, non-protein nitrogen, and the chloride determinations. The technique employed for the sugar was that of Folin's Modification of the Folin and Wu method of Whitehorn (17). The Klett-Summerson photo-electric colorimeter was used for the reading of all analyses with the exception of the chlorides. All analyses were completed within 4 hours. Benedict's qualitative method was used in the determination of the urine sugar. A Methylene Blue Test (18) was used in determining the presence of biliary pigments in the urine. This is not a precise method of determining bile pigments, but it reveals increases with sufficient accuracy for clinical purposes.

CLINICAL MATERIAL

Blood sugars were studied in 39 patients suffering from some acute manifestation of leprosy. The acute reactions or lepra fever are usually characterized by general symptoms such as fever (up to 40°C), chills, malaise and weakness, plus local findings of the skin (erythema nodosum or diffuse erysipeloid infiltration), of the nerve (neuritis), or of the lymph nodes (lymphadenopathy). We studied 24 cases in which the reaction was characterized by erythema nodosum, chills and fever, of which 4 cases were severely ill, 14 cases moderately ill, while 6 were mild, ambulatory cases. In

addition, we studied 13 cases in which the reaction was localized in tender, painful nerve trunks and 2 cases of leprous lymphadenopathy. We found that in all but the mildest cases, there was a definite increase in the fasting blood sugar.

The levels are listed below:

4 cases severe erythema nodosum:	range	138-168	average	154
14 cases mild " "	"	105-126	"	116
13 cases leprous neuritis	"	118-160	"	134
2 cases leprous lymphadenopathy	"	134-150	"	142

In order to show that these increases in blood sugar were not the result of dehydration, non-protein nitrogen was assayed in 20 of the patients undergoing acute lepra reactions with hyperglycemia and the range was found to be 22-40, and in 14 such patients the blood chlorides were measured and found to vary from 412-500.

The hyperglycemia associated with acute manifestations of leprosy differs from that associated at times with any of various acute infections in that the hyperglycemia usually described with other acute infections is essentially a rise in the glucose tolerance curve after a normal fasting sugar. In our cases, the fasting sugar was elevated. Attention should be called to the fact that patients with diabetes mellitus were excluded from the group and in no case has any patient in the group studied ever had any glycosuria.

After observing the elevation in fasting blood sugar in the 39 acute reactions studied, bile pigments in the urine were studied by means of the methylene blue test (18) in 44 acute reactions. The methylene blue test for bile pigments was found positive in 72.7 per cent of such cases, as compared to 50 per cent positive in 30 cases of leprosy not associated with acute reactions run at the same time. The interesting observation made from the methylene blue test was that seven patients who had previously had methylene blue tests negative for bile pigments in the urine had positive tests during the reaction, which reverted to negative again after the reaction was over. From this observation, it seemed quite likely that the hyperglycemia observed during acute phases of leprosy is probably related to metabolic functions of the liver.

For comparative purposes, during this study of hyperglycemia associated with acute forms of leprosy, fasting blood sugars were studied in 35 patients with only chronic manifestations of leprosy. The levels varied from 92-155 with an average of 111 for the group. As noted, the percentage of positive methylene blue liver function tests for bile pigments in the urine, is lower in the chronic (control) group. A series of 318 patients was reported by one of the

writers in 1940 which indicated that the basal metabolic rate is not influenced by leprosy (19).

DISCUSSION

The most common acute manifestation of leprosy is erythema nodosum, usually accompanied by chills and fever. In addition, there may also be erysipeloid reactions of the skin, painful neuritis or painful lymphadenopathy, which may occur separately or together. All of these acute manifestations of leprosy are associated with increase in the blood sugar and many of them with presence of bile pigments in the urine which suggest changes in hepatic function. The question arises, whether the hyperglycemia is part of the cause of erythema nodosum, or whether it is a by-product from some effect of the reaction. In an effort to determine whether hyperglycemia was related to the pathogenesis of erythema nodosum, neuritis, and lymphadenopathy in leprosy, 40 patients suffering from various forms of lepra fever were treated with protamine zinc insulin in daily doses of from 25 to 40 U. for three days at a time. The results are tabulated below

Severe erythema nodosum:		4 cases
Moderately improved	75 per cent	
Unchanged	25 per cent	
Moderate erythema nodosum:		15 cases
Greatly improved	53 per cent	
Moderately improved	47 per cent	
Mild erythema nodosum:		3 cases
Greatly improved	100 per cent	
Leprous neuritis		14 cases
Greatly improved	50 per cent	
Moderately improved	43 per cent	
Unchanged	7 per cent	
Leprous lymphadenopathy:		4 cases
Greatly improved	75 per cent	
Moderately improved	25 per cent	

It is interesting to note that in the course of treatment of 40 patients suffering from acute manifestations of leprosy with protamine zinc insulin in doses of 25-40 U. daily, in only one case was there any evidence of insulin shock. One patient with severe neuritis of both radial nerves who was unable to sleep regardless of what analgesia, sedatives, or narcotics were given had a fasting blood sugar level of 118, which was a high normal level that was the low-

est recording of any member of the neuritis group. Because no other treatment helped the neuritis, insulin was given despite the fact that there was no frank elevation of the blood sugar. The neuritis cleared up within 24 hours, but one evening after she had received 35 U. of protamine zinc insulin in the morning, she became very hungry and started to suffer from drowsiness and tremor. She was given some orange juice and a glass of milk and quickly recovered. While blood sugar determinations were made on most of the patients given insulin at the leprosarium, from the low incidence of insulin reaction among patients suffering with acute reactions of leprosy, it might even seem possible to give insulin empirically in institutions where laboratory facilities are more limited.

When another patient, who had been suffering from severe neuritis of both ulnar nerves, which had not been helped by any other treatment, was given 40 U. of protamin zinc insulin daily, he had complete relief from his pains, except for a short period every day after eating. His fasting blood sugar had been 140 before starting the treatment and dropped to normal levels; however, it is interesting that the temporary alimentary glycosuria after eating was associated with a brief return of the symptoms.

From the clinical improvement in acute symptoms of leprosy which is seen with the insulin treatment, it would seem reasonable to suppose that there is a disturbance in the carbohydrate metabolism associated with the formation of these reactions. From the experience at the Leprosarium, it seems that if insulin is given when the acute reaction is developing, symptoms are likely to subside rapidly without developing to any degree of severity. If the reaction is already severe when insulin is given, there is likely to be some clinical improvement, especially when the dose of insulin is relatively large, but, in general, a reaction that has developed fully is benefited much less by insulin treatment than one that is in the process of formation.

CONCLUSION

Leprosy is a chronic disease in which there are at times acute manifestations called leprous reactions or lepra fever. During these reactions the patient is acutely ill and shows systemic and local findings. The local lesions may be those of erythema nodosum, or, less often, erysipeloid reactions of the skin, painful neuritis, or painful lymphadenopathy. During these acute reactions there is an increase in the fasting blood sugar, and some evidence has been presented that a disturbance in carbohydrate metabolism is associated with the formation of the reaction, and that, therefore, parenteral insulin treatment is indicated.

References

(1) Aguirre, R. C. Experimental confirmation of the tuberculous nature of erythema nodosum. Semana méd. **38** (1931) 1673.

(2) Thompson, B. C. Erythema nodosum and cervical gland tuberculosis. Three illustrative cases. Brit. J. Tuberc. **30** (1936) 84.

(3) Wallgren, A. Erythema nodosum and pulmonary tuberculosis. Lancet. **234** (1938) 359.

(4) Pierret, R., Breton, A., and Lefebure, G. Erythema nodosum and phlyctenular keratitis; reflections of the variations of the tuberculous allergy in children. Paris méd. **29** (1939) 255.

(5) Lincoln, E. M., Alterman, J., and Bakst, H. Erythema nodosum in children. J. Pediat. **25** (1944) 311.

(6) Thorner, J. D. Erythema nodosum in childhood associated with infection by the *Oidium coccidiodes*. Arch. Pediat. **56** (1939) 628.

(7) Smith, C. E. Epidemiology of acute coccidioidomycosis with erythema nodosum. Am. J. Pub. Health. **30** (1940) 600.

(8) Loveman, A. B. and Simon, F. Erythema nodosum from sulfanilamide. J. Allergy. **12** (1940) 28.

(9) Simon, J. Contribution to the treatment of erythema nodosum. Therap. d. Gegenw. **82** (1941) 142.

(10) Poppel, M. H. and Melamed, A. M. Erythema nodosum. New England J. Med. **227** (1942) 325.

(11) Frankel, E. Erythema nodosum. A severe type in middle-aged women. Lancet. **248** (1945) 817.

(12) Sick, W. Blood sugar curves in acute febrile infections. München med. Wchnschr. **78** (1931) 609.

(13) Muir, E. Preliminary report on diasone in the treatment of leprosy. Internat. J. Leprosy. **12** (1944) 1-6.

(14) Faget, G. H., *et al.* The promin treatment of leprosy. A progress report. Pub. Health Rep. **58** (1943) 1729-1741.

(15) Faget, G. H. and Pogge, R. C. The therapeutic effect of promin in leprosy. Pub. Health Rep. **60** (1945) 1165-1171.

(16) Faget, G. H., and Pogge, R. C. Treatment of leprosy with diasone. New Orleans M. & S. J. **98** (1945) 145.

(17) Hawk, P. B. and Bergeim, O. Practical Physiological Chemistry. Philadelphia, P. Blakiston's Sons & Co., 9th ed.

(18) Meyers, C. P. Use of methylene blue in testing for bilirubin in the urine. J. Indust. Hyg. & Texicol. **27** (1945) 52.

(19) Ross, Sister, Hilary. Basal metabolism in leprosy. Internat. J. Leprosy. **8** (1940) 53.