AETIOLOGY OF ERYTHEMA NODOSUM IN CHILDREN

BY

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Erythema nodosum is considered by most authors to be a non-specific manifestation of hypersensitivity to various allergens, mainly bacterial (Collis, 1933; Röttnes, 1936; Spink, 1937; Wallgren, 1938a; Ernberg and Gabinus, 1939; Perry, 1944; Skiöld, 1945; Löfgren, 1946), although some still consider it to be a specific infectious disease (Miescher, 1948).

Of the infective agents responsible for the hypersensitivity, *Mycobacterium tuberculosis* is the commonest in childhood. Second in frequency is the streptococcus, the aetiological significance of which has been demonstrated by Collis (1932). Very few cases in childhood are due to hypersensitivity to other organisms. An exception to this is found in the parts of the U.S.A. where coccidioidomycosis is common, for about 11% of the children with this infection have an eruption similar to erythema nodosum (Smith *et al.*, 1946).

The relation of erythema nodosum to tuberculosis in children was noticed as long ago as 1872 (Uffelmann, 1872) but little attention was given to it until Ernberg (1921) published his theory and observations on the nature of this relation. The opinion that erythema nodosum is commonly a manifestation of primary tuberculous infection became accepted more generally as a result of the work of Wallgren (1927, 1928, 1930, 1931). Of 800 children with erythema nodosum whom he had seen by 1938 (Wallgren, 1938a) 95% had a positive tuberculin reaction. Reports on the tuberculin reaction of children with erythema nodosum have been published by many authors on the Continent (Göbel, 1933; Moro, 1934; Landorf, 1935; Debré *et al.*, 1938; Mallet, 1938; Nobécourt and Briskas, 1941; and many others).

Although it is known (Wallgren, 1938a) that the incidence of tuberculous infection in children with erythema nodosum varies from country to country, studies in the British Isles (Boganovitch, 1930; Begg, 1932; Collis, 1933; Forman and Whitwell, 1934; Thompson, 1939; Gray, 1945) and North America (Dickey, 1932; Brandon *et al.*, 1938; Lincoln *et al.*, 1944; Roddy, 1949) have been based on small series of cases only. The single exception is the study by Perry (1944), who determined the incidence of tuberculosis in 112 patients with erythema nodosum. Sixty-seven were children—in 29 (43.3%) the eruption was definitely related to tuberculosis, in 21 (31.3%) the relation was probable, and in 17 (25.4%) tuberculous infection was excluded.

The present paper concerns 100 children with erythema nodosum. It is presented because of the small number of similar observations in this country and in order to draw the attention of family doctors once more to the importance of recognizing erythema nodosum in children as a valuable sign of tuberculous infection.

Material

All the 100 children were seen and investigated in the Children's Department of the Royal Victoria Infirmary,

Newcastle-upon-Tyne, or at the Children's Hospital, Sheffield. Seventy were seen by the author and the information for the remaining 30 was obtained from their case notes. In 20 children a course of sulphonamides preceded the eruption by a period varying from 12 hours to 12 days. These children are included in the present series, as it is considered (Löfgren, 1945; Doxiadis and McLean, 1948) that erythema nodosum occurring after the administration of sulphonamides is fundamentally the same as that in which the eruption is spontaneous.

The age and sex incidence is shown in Table I. The low incidence after the age of 13 is without significance because older children receive treatment in other departments.

TABLE I.—Age and Sex Incidence of Erythema Nodosum

Age, Years Completed	No. of Children	Age, Years Completed	No. of Children
1	6	8	7
2	5	9	11
3	6	10	13
4	5	11	7
5	4	12	10
6	6	13	11
7	7	14	2

Boys 38. Girls 62.

The seasonal incidence is presented in Table II, and it can be seen that there is a smaller number of cases in summer and autumn.

TABLE II.—Seasonal Incidence of Erythema Nodosum

Month	No. of Children	Month	No. of Children
January	12	July	3
February	10	August	6
March	10	September	5
April	9	October	6
May	11	November	10
June	5	December	13

Results

All children were tested with tuberculin. The first test was either the application of tuberculin jelly on the skin or the intradermal injection of 0.01 mg. or less (0.005–0.01 mg.) of old tuberculin. If the test was positive no further tests were performed. If the reaction was negative then larger amounts of old tuberculin (0.1–1 mg.) were injected intradermally.

A positive reaction to tuberculin was found in 88 children (88%). In three of these the first test was negative or doubtful and all three showed a strongly positive reaction to 0.1 mg. of tuberculin. Of the 12 tuberculin-negative children, four were tested with 0.1 mg. and eight with 1 mg. or more of old tuberculin.

Of the 88 tuberculin-positive children, 59 (67%) had other evidence of active tuberculous infection. In 54 the radiograph showed marked undoubted unilateral enlargement of the hilar shadows, and in some of these there were opacities in the lung, on the same side as the hilar enlargement, consistent with the diagnosis of primary tuberculosis. Five children had cervical adenitis and in three the pus obtained by incision or aspiration contained *Myc. tuberculosis*.

Within three months after the appearance of erythema nodosum a pleural effusion developed in four of those children, there was an extension of the radiological signs in the lungs in two, miliary tuberculosis developed in one, and one child died from tuberculous meningitis.

Of the remaining 29 tuberculin-positive children, there were no radiological changes in 22, and doubtful changes in seven.

The relation of tuberculous infection to erythema nodosum is summarized in Table III. No further investi-

TABLE III.—*Relation of Erythema Nodosum to Tuberculous Infection*

Tuberculin-positive children	88
With other evidence of active primary tuberculous infection	59
Without or with doubtful other evidence of active primary tuberculous infection	29
Tuberculin-negative children	12
Total:	100

gations were made in the 12 tuberculin-negative children. The eruption followed a sore throat in five of them and scarlet fever in one.

In none of the 100 children was there any evidence of rheumatic infection, and in the 80 who were observed for at least six months after the eruption there has been no sign of involvement of the heart.

Discussion

The high incidence (88%) of positive tuberculin reactions in the 100 children with erythema nodosum is comparable to the incidence found by many Continental workers and is even higher than that in the only other recent series from this country (Perry, 1944).

It cannot be stated with certainty that the erythema nodosum was due to tuberculosis in all the 88 tuberculin-positive children. It may be said, however, that at least in the 59 (67%) who at the time of the eruption had other evidence of active tuberculous infection there was a close relation between the eruption and the infection. In the remaining 29 children (33%) the same relation probably existed.

These results show that in this country, too, most of the children with erythema nodosum are passing through their primary tuberculous infection. Any child therefore with erythema nodosum should be considered to have been recently infected with tuberculosis unless carefully performed tuberculin tests are negative. Because of the high degree of sensitivity to tuberculin of the tuberculin-positive children with erythema nodosum a jelly test is usually sufficient to elicit a positive reaction. If intradermal tests are used, the amount of old tuberculin in the first injection should never exceed 0.01 mg.

Special investigations were not made in the 12 tuberculin-negative children, and there is therefore no direct evidence that a streptococcal infection was the main aetiological factor, though a sore throat or scarlet fever preceded the eruption in six.

The absence of any demonstrable relation between erythema nodosum and rheumatic fever in the present series is worthy of emphasis. Some doctors still consider that erythema nodosum is "rheumatic" in origin and fail therefore to carry out any further investigations. Out of 800 children with erythema nodosum Wallgren (1938b) saw only one in whom the eruption was related to rheumatic fever. Löfgren (1946), in his study of 184 cases of erythema nodosum in adults, found that there was no evidence that erythema nodosum is connected with rheumatic fever; and Skiöld found a probable connexion in only five (1.4%) out of 354 adults with erythema nodosum. It is clear, therefore, that erythema nodosum is very rarely due to rheumatic fever.

Summary

Out of 100 children with erythema nodosum 88 had positive tuberculin reactions. In 59 of these there was an active primary tuberculous lesion. In the remaining 29 tuberculosis was probably the aetiological factor. In none of the children was there any connexion between erythema nodosum and rheumatic fever.

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POST-OPERATIVE THROMBOSIS*

INVESTIGATION OF A PROPOSED TEST FOR ITS PREDICTION

BY

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In a paper on intravascular thrombosis Cummine and Lyons (1948) claimed that by the examination of the post-operative coagulation time and estimation of the plasma fibrinogen-B they could foretell the onset of impending thrombosis. They further suggested that if the coagulation time as measured by the capillary tube method drops to four minutes, and if fibrinogen-B (an intermediate product in the change of fibrinogen into fibrin) can be demonstrated in the blood, then prophylactic anticoagulant therapy should be instituted.

In spite of the introduction of heparin and dicoumarol, thrombosis and embolism still contribute to the incidence of post-operative morbidity and mortality, and a simple test to determine which patients should be given anticoagulant drugs to prevent these complications is being widely sought. Investigation of a series of cases, using the proposed tests of Cummine and Lyons, was therefore undertaken.

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