Recent Investigations.—Serum proteins, total 7.6 g. per 100 ml. (albumin 5.1 g., globulin 2.5 g.); haemoglobin, 86%; white cells, 6,200 per c.mm.; E.S.R., 10 mm. (Westergren); blood urea, 40 mg. per 100 ml. An x-ray film of the chest showed dense calcification of miliary lesions. The E.C.G. showed clubbing of P waves.

Comment

There is no doubt that the administration of A.C.T.H. at the time of the acute lupus crisis was life-saving. The immediate response was similar to that reported by other people, but the eventual outcome is unlike any other case of equal severity so far recorded. Over two and a half years have elapsed since the advent of the original illness, and there is now no clinical or laboratory evidence of its activity.

Most people are agreed that acute disseminated lupus erythematosus is an example of a hypersensitivity reaction which in some cases may be associated with a tuberculous infection. However, Klemperer *et al.* (1941) noted the infrequency of arrested tuberculosis and the complete absence of active tuberculosis in 20 consecutive necropsies. Sequeira and Balean (1902) found a tuberculous focus present in 70% of their acute cases, as compared with 18% in their discoid form; but they commented on the rare occurrence of the acute disseminated disease among the large number of patients attending chest hospitals.

In the light of subsequent events it must be assumed that in this case a latent tuberculous focus was present. Whether it was the single sensitizing agent must remain a matter of opinion. It may be argued that the long remission induced by A.C.T.H. and maintained by streptomycin suggests a tuberculous aetiology. But the fundamental changes wrought in the host cannot be explained entirely by the response to a drug whose action is principally on the parasite. Long and Miles (1950) have shown that both A.C.T.H. and cortisone diminish bacterial allergy in guinea-pigs as measured by sensitivity to tuberculin. Rich *et al.* (1950) have found that the incidence of periarteritis and endocarditis produced by intravenous horse-serum injections in rabbits is greatly diminished when cortisone is administered. On the other hand, the known specific effects of these steroids on lymphocytes and fibroblasts may depress the natural resistance of the host.

It is suggested that in this case A.C.T.H. acted both as a non-specific and as a specific desensitizing agent; and that it also induced a profound depression of mesenchymal tissue, as demonstrated by the occurrence of miliary tuberculosis. Nevertheless, a favourable environment appears to have been created for the subsequent action of streptomycin. It may be, as Hart, Long, and Rees (1952) suggest, that the depression of sensitivity and the mechanism of chemotherapeutic action have some common factor.

Summary

A case of miliary tuberculosis in a case of acute disseminated lupus erythematosus is reported.

A possible mode of action by the drugs employed is suggested.

I wish to thank Dr. N. G. Hulbert for his kind permission and encouragement to publish this case, and for so kindly reading the original manuscript; Dr. Raymond Greene for his interest and comments; and the Honorary Editors of the *Proceedings of the Royal Society of Medicine* for allowing me to make use of the preliminary report of November, 1951. I would also like to congratulate the nursing staff of the Metropolitan Hospital, in particular Sister U. J. Young, whose sympathetic handling of the patient contributed so largely to her recovery.

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ERYTHEMA NODOSUM WITH BILATERAL HILAR GLAND ENLARGEMENT

A CLINICAL SYNDROME

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Numerous publications in recent years have thrown new light on the subject of erythema nodosum, and have done much to dispel earlier misconceptions. The view that the condition may occur as a response to a variety of diverse agencies, particularly bacterial and chemical, is now universally accepted. It is found predominantly in children and young adults, and, while primary tuberculosis is the most common cause, acute rheumatism is believed to be seldom associated with it.

As erythema nodosum is so often accompanied by pulmonary changes it should be a routine practice, wherever possible, to make an x-ray examination of the chest of all cases, and, if nothing abnormal is found, to repeat the examination a few weeks later. In cases in which there are positive findings subsequent examinations should be made at appropriate intervals until no further information of value is likely to be obtained.

This procedure has naturally led to the discovery of a number of cases of previously unsuspected primary tuberculosis; of more interest has been the discovery of six cases of bilateral hilar gland enlargement with no significant changes in the lung fields. The purpose of this paper is to report this latter group.

Case Reports

Case 1.—Woman aged 26. Developed typical erythema nodosum towards the end of May, 1951. Mantoux 1:100 positive. No chest symptoms. X-ray film on July 12 showed enlargement of both hilar and paratracheal glands (Fig. 1). Subsequent examinations showed gradual resolution, and by September 18 the appearances of the chest had returned to normal (Fig. 2).

Case 2.—Woman aged 26. Developed influenza-like illness with erythema nodosum in February, 1949. Mantoux 1:1,000 positive. No chest symptoms. X-ray examination

on February 24, 1949, revealed bilateral hilar gland enlargement, especially on the right (Fig. 3). Gradual resolution during following months. On October 26 resolution was not quite complete.

Case 3.—Woman aged 28. Developed erythema nodosum in December, 1949. Mantoux 1:100 positive. No chest symptoms. X-ray film on February 9, 1950, showed bilateral hilar gland enlargement (Fig. 4). Chest practically normal on July 5.

Case 4.—Woman aged 28. January, 1950: muscular pains, at first mild, becoming more severe, especially in right gluteal region. March–April, 1950: erythema nodosum with malaise, slight pyrexia, mild aches and pains. Mantoux 1:10,000 negative. (Tests at other strengths were not done.) E.S.R. 60 mm./1 hour (Westergren). On April 11, 1950, there was bilateral hilar gland enlargement (Fig. 5). Tooth extracted on May 2 for apical abscess: culture gave heavy growth of *Streptococcus*

viridans. September, 1950: tonsillectomy; culture, *Str. viridans*. Resolution complete on September 28.

Case 5.—Woman aged 37. Typical case of erythema nodosum in May, 1951. The X-ray appearances of the chest and subsequent progress were exactly like those of the above cases.

Case 6.—Woman aged 27. Admitted to hospital on February 24, 1950, with a history of pain in wrists, elbows, knees, and ankles of 10 days' duration. Erythema nodosum on legs for several days. Sore throat (history of recurrent sore throats). Throat swab at time of admission contained mixed flora with heavy growth of haemolytic streptococci. Mantoux test (March 8, 1952) 1:10,000 positive. X-ray film on admission showed bilateral hilar gland enlargement; subsequent examinations showed gradual return to normal.

(Since this paper was written we have seen three further cases of erythema nodosum in adults—one with bilateral and two with unilateral hilar gland enlargement.)

FIG. 1.—Case 1. Radiograph taken on July 12, 1951, showing enlargement of both hilar and paratracheal glands.

FIG. 2.—Case 1. Radiograph taken on September 18, showing return to normal.

FIG. 3.—Case 2. Enlargement of hilar glands, especially on the right.

FIG. 4.—Case 3. Bilateral hilar gland enlargement.

FIG. 5.—Case 4. Bilateral hilar gland enlargement.

Discussion

All the above cases occurred in relatively young women during the months of December to May. In none of the cases were there definite signs or symptoms referable to the lungs. There were no significant radiological changes in the lungs apart from the glandular enlargement. No case showed peripheral glandular enlargement or any other visceral manifestations of significance. The time of resolution varied to some extent, but it was usually complete within six months. In five cases the Mantoux test was found to be positive, and in one case negative at 1:10,000. Unfortunately, as the patients were almost all at home, more detailed examinations were not possible.

It seems probable that cases of this nature represent a special syndrome; the aetiology is uncertain. In all likelihood there were, during the period in question, further cases of a similar nature in Hull and district of which we were unaware. The total number of such cases throughout the country may therefore be quite considerable, and it is hoped that this brief report may stimulate interest in the problem.

In relation to the aetiological possibilities one must consider the known causes of erythema nodosum.

Tuberculosis.—Primary complex can be excluded, as bilateral hilar gland enlargement of this nature is not consistent with our present conception and experience of primary tuberculosis. The relatively rare adult glandular tuberculosis is unlikely for similar reasons.

Sarcoidosis.—There was no clinical evidence of sarcoidosis in any of our cases, and no bone changes were seen in radiographs of the hands or feet. No special tests, such as the Kveim test, were done. Positive tuberculin tests do not exclude sarcoidosis, though a strongly positive reaction is rather against such a diagnosis (cases of sarcoidosis tend to be negative or weakly positive reactors). The complete resolution of the lesions in such a relatively short time, while not excluding sarcoidosis, is not in favour of it.

Bacterial or Virus Infection.—Streptococcal infections are regarded as being an occasional cause of erythema nodosum, and it seems quite possible that these cases, from their nature, may be related to some bacterial or perhaps virus infection. There is, as yet, no definite confirmation of this.

Sulphonamides or Other Chemical Agents.—No drugs of this nature had been given in any of these cases.

What is the relationship of our cases to similar cases previously reported? Kerley (1943), discussing the aetiology of erythema nodosum based on a study of the disease in 37 adults with an average age of 21, found eight cases with enlarged bronchial glands and without pulmonary

changes. It seems probable that some of these eight cases are similar to ours, although this group is not discussed in detail. He believes that in some cases the radiological appearances are identical with those described in sarcoidosis.

Middlemiss (1949), reporting on 124 cases, found 56 with pulmonary changes, only one of which bears any possible relationship to ours. He regards his case as non-tuberculous, although the Mantoux reaction was strongly positive at 1:10,000.

Sterling (1950) reports two cases of erythema nodosum with bilateral hilar gland enlargement, the x-ray appearances being, so far as can be determined, identical with our cases. In both instances the Mantoux reaction in all strengths was negative. The serum of each patient was found to possess tuberculin-neutralizing properties. In spite of this he concludes that a diagnosis of sarcoidosis is not justified. He suggests that this is a peculiar clinical syndrome which merits further investigation.

Crawley (1950) discusses three cases of erythema nodosum with bilateral hilar gland enlargement. The Mantoux reaction was negative in two cases, and positive (1:100) in one. While no histological proof could be obtained, Crawley suggests that his cases could be regarded as sarcoidosis.

Löfgren (1946) regards his cases of bilateral hilar gland enlargement, with a negative tuberculin reaction or a reaction of 1:1,000 or 1:100, as probably sarcoidosis.

Johnson, Hanson, and Good (1951) found hilar adenopathy in 9 out of 100 consecutive cases of erythema nodosum; in eight of them the adenopathy was bilateral. They suggest that hilar adenopathy has not been generally recognized as an accompaniment of erythema nodosum. Follow-up films of five patients were available; in three the hilar enlargement had disappeared in from one to seven months. They draw no conclusions regarding the aetiology.

Summary

Six cases of erythema nodosum are described in young adults with bilateral hilar gland enlargement and no other pulmonary changes; the possible aetiology is discussed. The condition seems to warrant the title of a clinical syndrome, and collation of further similar cases is desirable.

We wish to express our indebtedness to Dr. N. Gebbie, formerly M.O.H., Hull, and to those general practitioners who were kind enough to assist us in investigating their cases.

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