When this patient was shown here in 1954 the point was made that lymphocytoma was a very benign condition and that she had had it for thirty years and no harm had come of it. It was not until last year, thirty-six years after the onset of the condition, that harm did come of it when suddenly a lymphosarcoma appeared and grew with alarming rapidity.

REFERENCE Pegum J S (1954) *Proc. R. Soc. Med.* 47, 1061

Ehlers-Danlos Syndrome Associated with Streptococcal Hypersensitivity

G M Cochrane MB (for D I Williams FRCP)

M M, female, aged 36. Housewife

History: She was well until end of January 1961 when she had acute inflammation of the right ankle for forty-eight hours followed by effusions in both knees and similar transitory acute arthritis of the left ankle. Treated with Disprin gr 60 daily for three weeks.

On admission 1.3.61: Temperature 100° F; pulse regular 105; œdema of both legs; œdema of right thigh with raised erythematous area and bulla at centre; red tender nodule on left elbow; slight effusion left knee. Fever continued over the next three weeks and she lost 12 lb in weight. Extensive œdematous red lesions developed over the buttocks, with blistering followed by ulceration. With change of position similar lesions appeared at sites of pressure.

25.3.61: Bilateral pleural effusions; in all 50 oz were aspirated from right and 55 oz from left pleural cavity. Pericardial rub heard. Œdema of both legs, slight proteinuria and hypoalbuminuria.

Prednisone 60 mg daily, chlorothiazide 1 g b.d. on three days a week and high protein diet given; œdema disappeared, plasma proteins returned towards normal, general condition improved and weight was regained. Reduction of prednisone to 20 mg daily was followed within seventy-two hours by localized œdema of vulva and right side of face. On prednisone 60 mg daily fresh lesions continue. There seem to be five stages in their natural history: (1) *In dependent* areas local œdema, pitting on pressure. (2) After two to three days: tender, red, raised patches. (3) In some lesions there have been bullæ, which frequently burst leaving moist red bases unless secondarily infected. (4) Over the next ten days lesions become dusky, in parts yellowish and with resolution of œdema striæ distensæ. (5) Within three weeks lesion flat, striated with telangiectasia.

Investigations: Hb 85% (12·6 g/100 ml). W.B.C. 11,000 (neutros. 8,250, lymphos. 2,310, monos. 440, eosinos. 0). E.S.R. 22 mm in one hour (Wintrobe); has fallen to 2 mm in one hour. Throat swab: Group A hæmolytic streptococci. Anti-streptolysin 'O' titre: 2.3.61, 480 units; 13.5.61, 820 units; 10.6.61, 495 units.

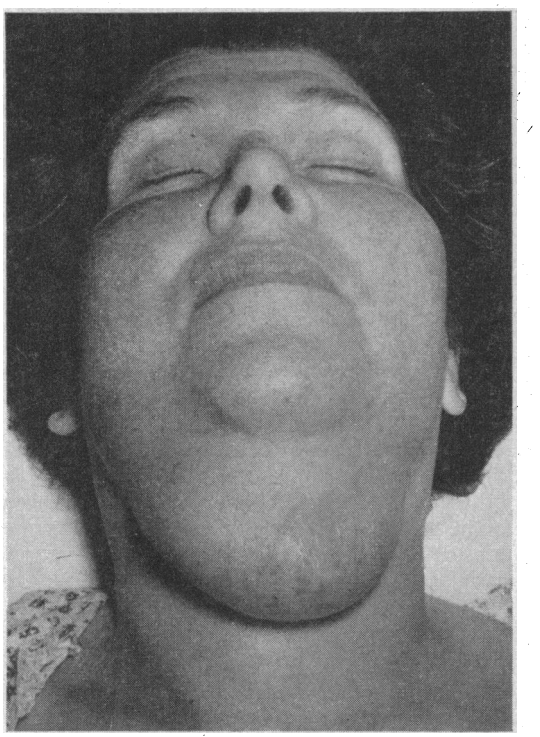

Fig 1

Urine protein 60 mg/100 ml. No proteinuria during past ten weeks.

Plasma proteins: Total 5·1 g/100 ml. Albumin 23%, α_1 6·5%, α_2 27%, β 14·3%, γ 29·2%. Repeated estimations show change to normal electrophoretic pattern, 29.5.61. Pleural fluid: Numerous pus cells; protein 5 g/100 ml.; culture – no growth; polys. 80%; lymphos. 20%. Chest X-ray (23.3.61): Bilateral pleural effusion. C reactive protein, Rose Waaler, L.E. cells, blood cultures, antinuclear factor, liver function tests, serum transaminase, serum cholesterol, glucose tolerance curve, serum uric acid, blood urea, W.R. and ECG were all normal.

Biopsy of skin lesion shows moderate hyperkeratosis. Some of the cells of the epidermis show hydropic degeneration and in some areas there is keratic plugging. The dermis is patchily infiltrated with chronic inflammatory cells mainly centred around the skin appendages which also show considerable surrounding fibrosis. There is no abnormality of blood vessels. There is fragmentation and degeneration of elastic tissue elements.

Biopsy of unaffected skin: Elastic tissue appears abnormal, being increased in amount and clumped into small aggregates.

Comment: This has seemed to us an unusual disease, beginning with acute arthritis and associated with fever, loss of weight, abnormal plasma protein pattern, with increase in α_2 and γ fractions and low albumin, œdema, pleural effusions and skin lesions, some of which finally look like necrobiosis lipoidica.

The absence of L.E. cells, the poor response to prednisone in a dose below 60 mg daily, and the absence of antinuclear factor in the serum make systemic lupus erythematosus unlikely. Polyarteritis nodosa has not been evident in the skin biopsies, the patient is normotensive and there is no eosinophilia. It may be significant that the antistreptolysin titre was high at 480 units, and rose to 820 units, and has now fallen to 495 units.

The lesions seem to be related to local pressure. When she sat in bed they appeared over the buttocks, elbows, and shoulders. She was nursed on her side and developed similar lesions over her hips. When lying prone she developed œdema over the sternum, supraclavicular triangles, abdomen, right breast, and right side of the face – the side on which she preferred to lie most of the time. Fig 1 shows the large baggy swelling below her chin – developed in a dependent area. At first there was local œdema, which in distensible areas was considerable, and after two to three days there was a raised red centre. Fig 1 is a later stage showing a very œdematous area which is resolving; the striæ distensæ and telangiectasia may be seen. Finally the lesion becomes flat after three or four weeks, and the skin appears atrophic.

Dr T M L Price: This seems to be a systemic disorder though her general health has been surprisingly good except when she had pleural effusions. I doubt if steroid therapy explains her healthy appearance.

The lesions look quite different according to whether the skin breaks down or not, and whether scarring occurs; I think they are different in kind as well as varying in severity. The first manifestation of most of the lesions, however, is a collection of subcutaneous fluid, and this seems to damage the skin. The lesions usually appear in dependent areas and are more severe when subjected to pressure.

Apart from the diagnostic problem, suggestions about treatment would be appreciated. The illness is of long standing and causes considerable distress, particularly in view of her good general health.

Dr H Haber: I believe this patient has an Ehlers-Danlos syndrome with angioneurotic œdema.

Dr I B Sneddon: I think this is a combination of the Ehlers-Danlos syndrome and urticaria. It would be worth trying antihistamines in a high dose to see if the swellings can be suppressed. I have seen penicillin urticaria in a known case of Ehlers-Danlos syndrome where the clinical picture was very similar to the present case and the weals and swellings lasted many weeks. This diagnosis would not explain the attack of pleurisy.

The President: Did your patient's condition clear up with antihistamine?

Dr I B Sneddon: My patient did clear up with antihistamines but the duration of individual lesions was far longer than usual and she had the same pendulous swelling of the neck.

The President: I think most people would agree that this patient had early manifestations of Ehlers-Danlos syndrome.

Dr D I Williams: I saw this patient a few weeks ago and thought she had a very curious condition. I am not sure that since that time I have advanced any further towards a diagnosis. The suggestion that she has Ehlers-Danlos syndrome with some other disease superimposed is interesting, although I find it hard to believe. Certainly the histology would support the suggestion. Dr Sneddon seems to be the only Member who has seen anything resembling this case, and his patient had urticaria. To try antihistamines would seem to me to be sense, although the corticosteroids work more dramatically in cases of urticaria than has happened here. I can make no intelligent suggestion of a diagnosis to include the bizarre skin lesions, very painful joints and the pleural effusion. There is no evidence to clinch a diagnosis of vasculitis. The streptolysin titre is very high, and it is tempting to believe that this is a curious reaction to the streptococcus or its products.

POSTSCRIPT (19.10.61): Following Dr Sneddon's suggestion, since May 19, 1961, she has been treated with chlorpheniramine maleate 16 mg daily and prednisone was gradually withdrawn. No further lesions appeared. She was discharged on July 7, 1961, and remains well. – G M C

The following cases were also shown:

(1) Epiloia
(2) Inveterate Papular Urticaria
Dr Brian Russell

(1) Urticaria Pigmentosa with Bone Changes
(2) Smokers' Keratosis
(3) Lichen Nitidus
(4) Linear Eruption
Dr J S Pegum

Livedo Reticularis (Primary)
Dr P M Deville

Subacute Systemic Lupus Erythematosus: Porphyria
Dr C F H Vickers (for Dr I B Sneddon)

Reticular Livedo with Cerebrovascular Lesions
Dr R E Church

Kyrle's Disease
Dr H M Drummond (for Dr C M Ridley)