THREE CASES OF COLLAGEN DISEASE TREATED WITH CORTICOIDS

BY

D. G. RICHARDS, M.D., M.R.C.P.*Senior Registrar, Queen Elizabeth Hospital, Birmingham*

Since Klemperer *et al.* (1941) first coined the term "diffuse collagen disease" it has become customary to group together as disorders of collagen tissue such seemingly diverse conditions as rheumatic fever, rheumatoid arthritis, disseminated lupus erythematosus, diffuse scleroderma, dermatomyositis, and polyarteritis nodosa. In all of these conditions there are widespread lesions in the connective tissues, and it is the extracellular components of the latter, the collagen fibrils and the intermediate ground substance, which are chiefly affected. It is because of the widespread network of delicate collagen tissues in the walls of small blood vessels, beneath the endocardium and the lining endothelium of synovial and serous membranes, that the collagen diseases may have many features in common. Therefore, extensive vascular lesions, arthritis, endocarditis, pericarditis, and pleurisy are all frequent manifestations. However, in spite of closely similar anatomical and pathological features, it has never been possible to demonstrate any aetiological relationship between individual members of the group. They are all distinct clinical entities, and diagnosis, even of the rarer types, often presents very little difficulty. Sometimes, however, patients suffering from the rarer collagen disorders may present with an extremely acute illness in which many of the more characteristic features may be absent or inconspicuous. It is in these instances that diagnosis may be very difficult.

The knowledge that many of these cases can be controlled by the administration of corticoid drugs has made early diagnosis of the greatest importance.

The case histories of three patients are presented below, to illustrate the difficulties in diagnosis in these very acute cases and to show how the administration of corticoids may preserve life, and how their continued administration may maintain reasonably good health for prolonged periods.

Case 1

A married woman aged 54 was first admitted to the Queen Elizabeth Hospital on July 16, 1951. She had been ill for four months with severe joint pains and heavy attacks of sweating. Two weeks before admission her symptoms became worse and she developed severe pain along the left costal margin.

On examination she looked very ill and had a temperature of 101° F. (38.3° C.). There was symmetrical swelling of the wrist-joints and of the small joints of the hands. The other joints appeared normal, but movements of the shoulders, ankles, and knees were painful. The spleen was just palpable, but the heart, lungs, central nervous system, and urine were all normal.

After a few days in hospital her condition deteriorated and she developed almost continuous pyrexia from 104 to 105° F. (40 to 40.6° C.). The pain in the chest became more severe and the respiratory rate rose to 40 a minute. Moist rales were heard over both lung bases, and there was clinical and radiological evidence of small bilateral pleural effusions. The pyrexia failed to respond to aureomycin and the patient was given salicylates.

After a few doses, however, there was a precipitate fall in temperature to subnormal levels and the patient became

desperately ill with peripheral circulatory collapse and anuria. These symptoms lasted for 48 hours after the salicylate was discontinued, and then the temperature returned to its previous high level.

The agglutination reactions and blood cultures were negative. The blood showed an orthochromic anaemia (haemoglobin 84%) and a total white count of 5,700 per c.mm. (neutrophil polymorphs 79%). The sedimentation rate was high (54 mm. in the hour, Wintrobe), and estimation of the serum proteins showed a low albumin (2.2 g.%), and markedly raised gamma globulin (3.0 g.%) and fibrinogen (0.47 g.%).

The diagnosis on admission had been rheumatoid arthritis, but the severity of the illness, the marked pyrexia, and the inconspicuous joint changes, together with the appearance from time to time of a central facial erythema, suggested the possibility of disseminated lupus erythematosus.

Treatment with cortisone was begun on August 3, and 200 mg. was given daily for five days and then 75 mg. for a further 10 days. The temperature fell to normal within twenty-four hours and the patient's condition rapidly improved. However, on 75 mg. daily the temperature was not completely controlled, and rapidly returned to its previous level when the drug was discontinued. A.C.T.H., 30 mg., was then given daily by intramuscular injection, and this rapidly and completely controlled the pyrexia and all the symptoms.

After three weeks A.C.T.H. was discontinued and there was no relapse. The patient left hospital on October 3 and remained in good health until April, 1952, when pyrexia and joint pains returned. This relapse responded rapidly to a fortnight's course of A.C.T.H.

She remained well until December, when there was a return of severe arthralgia and high temperature. She was readmitted to hospital in January, 1953, and the symptoms were controlled on this occasion with cortisone. Relapse was rapid when the drug was discontinued, and since April, 1953, she has been on continuous maintenance therapy.

She is now on 100 mg. of cortisone daily, but pyrexia and joint pains return within twenty-four hours if any attempt is made to reduce this dose. On cortisone she enjoys reasonably good health and is able to do a full day's work looking after a grocer's shop. Her weight has increased by almost 3 st. (19 kg.) since treatment was begun in July, 1951.

Although symptoms are in abeyance the sedimentation rate is still raised (50 mm. in the hour, Wintrobe). The serum proteins remain abnormal, but less so than previously. The only abnormal clinical finding is a scaly red rash on the forehead, cheeks, nose, and chin. This has been present on and off for twenty years and was formerly regarded as acne rosacea. It was not in evidence during the initial acute illness, and tends to disappear during a relapse and to become more pronounced when the symptoms are controlled by cortisone.

The diagnosis of disseminated lupus erythematosus has been substantiated by the finding of lupus erythematosus cells in the peripheral blood. The differential sheep-cell agglutination tests gave a result in the lower range of significance (ratio 1:16). The direct Coombs test was negative.

Case 2

A girl aged 16 had enjoyed good health until July, 1952, when she began to complain of pain and stiffness in the feet and ankles, and later both knees, hands, elbows, and shoulders were affected. She was treated with phenylbutazone, but proved to be sensitive, and was admitted to another hospital with pyrexia, rash, and leucopenia. She remained as an in-patient for seven weeks and was discharged home in January, 1953. There was no improvement in the joint pains and stiffness, and her weight had decreased by nearly 3 st. (19 kg.) since the onset of the illness.

Her condition remained stationary until May, when she developed a sore throat and became acutely ill with severe pain in the central and left chest. She had difficulty in breathing, had marked pyrexia, and was vomiting. Three days later, on May 18, she was admitted to the Queen Elizabeth Hospital. She was desperately ill with a temperature of 104.6° F. (40.3° C.) and a respiratory rate of 54 a minute. There was generalized tenderness of the limbs and abdomen, and the slightest movement of the trunk or limbs caused severe pain. The small joints of the hands were slightly swollen, but all the other joints appeared normal. The skin of the fingers and backs of the hands was thickened, glossy, and unduly tethered to the underlying tissues.

The pyrexia and chest pain persisted, and two days after admission a pleural friction rub was heard in the right axilla, and shortly afterwards a pericardial friction rub became audible. A chest x-ray film showed a small left pleural effusion and an enlarged cardiovascular shadow strongly suggestive of pericardial effusion.

Investigations showed a marked orthochromic anaemia (red cells 3,080,000 per c.mm. and Hb 60%) and a total white-cell count of 13,400 per c.mm. (neutrophil polymorphs 83%). The sedimentation rate (Wintrobe) was 63 mm. in the hour. Agglutination reactions and blood cultures were negative, but the serum proteins were abnormal, the gamma globulin (4.2 g.%) and fibrinogen (0.74 g.%) being greatly increased. An E.C.G. showed flat T waves in all leads, but the P-R. interval was normal. Lupus erythematosus cells were not found in the peripheral blood.

A diagnosis of "diffuse collagen disease" was made, and treatment with cortisone, 100 mg. daily, was begun on May 20. Progress was excellent, and the contrast between the patient's condition at the end of a week's therapy with that of her dangerously ill state on admission was remarkable. The generalized pains disappeared within a few days, but the temperature took eight days to reach normal levels. The pericardial and pleural friction quickly disappeared, but the tachycardia subsided slowly over a period of several weeks. Attempts to reduce the dose of cortisone below 75 mg. daily resulted in a recurrence of arthralgia and pyrexia. However, aspirin (60 gr.—4 g.—daily in divided doses), given as a "cortisone sparer," enabled the maintenance dose of cortisone to be gradually reduced to 37.5 mg. daily, without any further recurrence of symptoms.

The patient went home on August 12 after three months in hospital. She is still (March, 1954) on cortisone, 37.5 mg., and aspirin, 60 gr. (4 g.), daily, and is back at work as a clerk. She now gets only occasional joint pains, and has put on almost 3 st. (19 kg.) in weight since treatment with cortisone was begun.

The skin of the fingers and backs of the hands is thickened and inelastic, changes which were noted during the initial acute illness. These changes are now much more marked and are apparent, but to a less degree, in the skin of the arms, face, and upper chest. After leaving hospital it was discovered that the patient had noticed that for the past three years her fingers would become very blue on exposure to cold. It would seem that the Raynaud phenomenon is one manifestation of a diffuse scleroderma. There has been, as yet, nothing to indicate involvement of the oesophagus, heart, or lungs, or of any other of the internal organs. Although the systemic symptoms are controlled the dermal changes have advanced in spite of cortisone therapy. Apart from slight stiffness of the fingers the scleroderma has not given rise to much disability, but painful cracks and fissures have appeared in the atrophic skin over the finger-tips.

The sedimentation rate remains high and the serum protein levels are still abnormal, although the gamma-globulin fraction (3.7 g.%) is less elevated than formerly. The blood count has returned to normal. Typical lupus erythematosus cells have not been seen, but pre-lupus erythematosus cells are reported in the peripheral blood. The differential sheep-cell agglutination test gives a result outside the range of significance.

Case 3

A 53-year-old housewife has suffered from typical rheumatoid arthritis for the past 23 years. The condition affects practically all the peripheral joints, but especially the hands and knees. Early in 1953 there was a sharp exacerbation of the arthritis, which was treated with phenylbutazone. In June, 1953, she had improved enough to go on holiday, but shortly after returning she became ill with a high temperature, dry cough, and severe stabbing pain in the left chest. The condition did not respond to full courses of penicillin and chloramphenicol, and on August 7 she was admitted to the Queen Elizabeth Hospital. She was very ill, thin, and anaemic, with a temperature of 103° F. (39.4° C.) and marked tachycardia. The wrist-joints and small joints of the hands were swollen and deformed, with ulnar deviation. The knee-joints were slightly swollen, and movements of these joints and of the elbows, shoulders, and ankles were restricted and painful. The respiratory rate was raised to 30 a minute, but the lung fields were clear. There was no orthopnoea and no peripheral oedema or rise in venous pressure. The blood pressure was normal, but the heart was enlarged clinically. The sounds were normal and there were no murmurs. The spleen was not palpable, but the liver was very tender, the edge being easily felt four fingerbreadths below the costal margin. The central nervous system and urine were both normal.

The pyrexia continued, and after a few days the heart developed gallop rhythm and a loud pericardial friction rub was heard. A little later moist rales and a pleural friction rub were heard over the lower lobe of the left lung. The liver remained enlarged and tender, and the spleen now became palpable.

Investigations showed an orthochromic anaemia and leucopenia (red blood cells 3,240,000 per c.mm., haemoglobin 66%, and white cells 3,300 per c.mm.) A chest x-ray film showed clear lung fields, but the cardiothoracic ratio was increased (57%). Agglutination reactions and blood cultures were negative, but the sedimentation rate was raised 41 mm. in one hour (Wintrobe). Serum protein estimations showed a low normal level of albumin (3.5 g.%) and a raised globulin fraction (4.7 g.%).

At first it was thought that the condition might be an obscure form of hepatitis, possibly a toxic reaction to phenylbutazone. The patient was put on a high-protein diet with supplemental vitamins, and a further course of penicillin was tried, without, however, any effect on the pyrexia. A blood transfusion of 3 pints (1.7 litres) was given for the anaemia. After the development of pericarditis and pleurisy, the diagnosis was revised to "generalized collagen disorder," and this diagnosis was supported by the finding of lupus erythematosus cells in the peripheral blood.

Treatment with A.C.T.H. was begun on August 12. This was given in the form of A.C.T.H. gel, 60 units twice daily by intramuscular injection. After two days the dose was reduced to 40 units twice daily, and after a further three days to 30 units twice daily. There was a prompt fall in the temperature. Unfortunately, on August 21 A.C.T.H. had to be discontinued because of the development of considerable oedema and hypertension, and there was an almost immediate recurrence of pyrexia. After three days A.C.T.H. was restarted, but once more had to be discontinued because of oedema and hypertension. Cortisone, 100 mg. daily by mouth, was substituted on August 27, but, although the fluid retention and hypertension were less marked on this drug, the temperature was not so dramatically controlled as by A.C.T.H., and only gradually subsided to normal levels during the ensuing three weeks. During this time the patient's general condition gradually improved and the pleural rub disappeared. Small staphylococcal ulcers and abscesses developed over the lower back and buttocks, and were treated by a course of aureomycin. After seven weeks in hospital the patient improved sufficiently to be allowed up, but gallop rhythm and pericardial friction were still

audible from time to time. She went home on October 3 on a maintenance dose of 100 mg. of cortisone daily, and since then she has been seen for review at approximately monthly intervals. An attempt to reduce the daily dose of cortisone below 75 mg. resulted in a prompt return of pyrexia. Considering the severity of her recent illness, her condition now is very satisfactory and she is able to lead a fairly normal, but restricted, life.

On 75 mg. of cortisone daily the arthritis is less troublesome than it has been for some years, although the joints remain stiff and deformed. She is breathless on slight-to-moderate exertion and there is still some oedema of the feet and ankles. The blood pressure varies between 160/100 and 185/120 mm. Hg, and moderate tachycardia and cardiac enlargement are still present. A systolic murmur is audible at the cardiac apex, but the pericardial friction has disappeared. The lungs are normal both clinically and radiologically, but the spleen cannot be felt and the liver is much smaller than formerly. The urine has remained normal throughout the illness. The sedimentation rate remains high (33 mm. Wintrobe) and the serum proteins abnormal. The blood still shows a mild orthochromic anaemia, less marked than before (red blood cells 3,850,000 per c.mm., haemoglobin 80%), but the white-cell count is normal. The electrocardiograph shows a well-marked right bundle-branch block. Typical lupus erythematosus cells are still reported present in the peripheral blood. The differential sheep-cell agglutination test gives a result outside the range of significance.

Discussion

These three patients presented during very acute episodes of their illnesses. On admission to hospital they were all desperately ill with marked pyrexia and joint manifestations. All three developed pleurisy, and two had pericarditis. In each case the sedimentation rate was much raised, and the serum proteins were abnormal, with marked elevation of the gamma-globulin fractions. The blood counts showed an orthochromic anaemia and the total white-cell counts were low in proportion to the degree of pyrexia. Case 1 was at first thought to have severe rheumatoid arthritis, but the rather insignificant joint changes were not proportionate to the severity of the illness, and the appearance of a central facial erythema suggested a clinical diagnosis of disseminated lupus erythematosus. This was later substantiated by the finding of lupus erythematosus cells in the peripheral blood. Case 2 on admission to hospital was suspected of having acute rheumatic carditis and pericarditis, but the absence of valvular lesions, and the changes in the skin of the hands, led to a diagnosis of acute diffuse scleroderma. Case 3 had suffered from typical chronic rheumatoid arthritis for more than 20 years. The extremely acute episode with high pyrexia, pleurisy, and pericarditis suggested a diffuse collagen disorder. Lupus erythematosus cells were found in the peripheral blood, and their presence probably means that this is a case of systemic lupus erythematosus without the typical skin changes.

Reports in the literature on the use of corticoids in the treatment of the rare collagen disorders are not common and most refer to disseminated lupus erythematosus. In untreated cases the natural history is marked by spontaneous exacerbations and remissions. These fluctuations are unpredictable, and not infrequently a patient with chronic symptoms may suddenly become desperately ill with an acute crisis of the disease. Similar acute exacerbations may occur in the other collagen disorders. If untreated the prognosis is poor, although very occasionally these very acute attacks may subside without special therapy. The outlook is much more favourable if corticoids are used in treatment, and Dubois *et al.* (1952) believe that nearly all cases will respond so long as the hormones are pushed to the point of producing the features of a Cushing syndrome. The three patients whose case histories are described above were all admitted to hospital in an acute crisis, and were all so ill that a fatal outcome seemed likely. In each, response to corticoids was marked, and the hormones were probably life-saving.

In the long-term maintenance therapy of the collagen disorders the value of corticoids is less certain, and the variable course and duration of these disorders make evaluation of therapy very difficult. Jessar *et al.* (1953) reviewed 323 cases of disseminated lupus erythematosus not treated with corticoids (44 of their own cases and 279 collected from the literature) and found that approximately 20% survive for periods in excess of five years from the onset. Dubois *et al.* (1952) found the average life expectancy of patients with this disease to be 22 months. Bundick and Ellis (1951) reported 26 cases in which the average life span was four and a half years. In a report of nine cases of disseminated lupus erythematosus treated with cortisone, Johnson and Meyer (1952) conclude that this drug is usually effective in the control of symptoms and signs, but that relapse usually takes place on cessation of therapy. Tumulty and Harvey (1952) believe that patients with significant renal involvement are often made worse by treatment with corticoids.

Soffer and Bader (1952) treated 18 patients with disseminated lupus erythematosus with A.C.T.H. and/or cortisone for periods of from 3 to 20 months; of these, 6 had died at the time of their report and 12 are living, of whom 8 require maintenance therapy. They believe that, although no actual cures result, some patients may be maintained indefinitely in a state of remission by treatment with corticoids. Cohen and Cadman (1953) treated five cases of systemic lupus erythematosus with cortisone and A.C.T.H. for periods ranging from 8 to 30 months. The response was excellent in one case and satisfactory in the others. They considered that the more severe the systemic features of the disease the more dramatic is the immediate response to treatment and the more satisfactory is the long-term improvement.

The three cases reported in this paper have been on continuous cortisone therapy for 12, 10, and 7 months respectively, and all are maintained in reasonably good health. Cases 1 and 3 suffer an immediate relapse if an attempt is made to reduce the maintenance dose. Case 2 has remained on a steady dose of 37.5 mg. of cortisone daily since leaving hospital, and she also takes 60 gr. (4 g.) of aspirin daily as a "cortisone-sparer." In spite of cortisone the sclerodermatous changes are gradually becoming more pronounced, and recently trophic lesions have developed in the skin over the finger-tips. In all three cases the symptoms of the disease are suppressed, but the sedimentation rates remain high, and the serum protein abnormalities are still present. In each case there has been an improvement in the blood count during treatment, but in Cases 1 and 3 lupus erythematosus cells can still be found in the peripheral blood.

While on corticoids the patients have been subjected to regular clinical and biochemical review, and they have taken a low-salt diet with additional potassium in the form of potassium chloride, 6 g. daily by mouth. In only one patient have there been any important side-effects to therapy. Case 3 while on A.C.T.H. developed retention of sodium chloride and water, with hypertension severe enough to lead to discontinuance of the drug. On cortisone, these effects were less marked but still troublesome, and there is still considerable hypertension on a maintenance dose just sufficient to control symptoms. After three months on cortisone Case 3 developed severe pain in the back, and x-ray examination of the lumbar spine revealed generalized osteoporosis with partial collapse of lumbar vertebrae 2, 3, and 5. Cortisone may have been the responsible agent, or it may have aggravated a pre-existing menopausal osteoporosis. This patient has suffered also from recurrent staphylococcal abscesses, and it is possible that cortisone may be responsible for the delayed healing of these abscesses.

Summary

The case histories are described of three patients who were admitted to hospital during extremely acute episodes of generalized collagen disease. The dramatic effect of corticoid drugs in controlling the acute symptoms is illustrated.

Each patient has been maintained in reasonably good health by the continued administration of cortisone.

I am grateful to Dr. Ernest Bulmer for permission to publish Cases 1 and 2, and to Dr. A. G. W. Whitfield for Case 3, and to both for their encouragement and helpful criticism. I am indebted to the late Dr. A. L. Peeney, who undertook the pathological investigations.

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RESULTS OF A PLANNED ATTACK ON CARCINOMA OF THE VULVA

BY

STANLEY WAY, F.R.C.O.G.

*Gynaecologist, Newcastle Regional Cancer Organization;
Associate Surgeon, Gynaecological Department, Royal
Victoria Infirmary, Newcastle-upon-Tyne*

In 1939 during the course of a discussion at the Royal Society of Medicine on the treatment of carcinoma of the vulva, F. J. Browne suggested that since this was a fairly uncommon disease the results might be improved by concentrating all the cases in the hands of a few surgeons, who might thereby gain greater experience in handling the disease than if the cases were scattered in various clinics all over the country, usually in ones and twos.

My interest in the disease was aroused by my former chief, Clifford White, who suggested that a study of it might prove useful, especially as the incidence appeared comparatively high in Newcastle-upon-Tyne.

The more academic aspects of that study I have reported elsewhere (Way, 1951), but, briefly, the research showed that the previously poor results were due not only to lack of experience on the part of those responsible for its treatment but also to the fact that standard treatments at that time were based on unsound pathological and anatomical principles. The removal of the vulva was insufficiently wide in most cases to prevent recurrence, and the node dissections were not extensive enough to deal with the metastases.

As a result of this study, I devised the extended radical vulvectomy and node dissection which I have described elsewhere in full (Way, 1951), but which in brief consists of the complete removal of the vulva from the mons to the anus, extending deep enough to expose the pubic bones and their associated muscles; the excision of wedges of skin from the groins and saphenous regions with the underlying lymph nodes which remain undetached from the skin during the operation; the division of the inguinal ligament; and the removal of the external iliac lymph nodes as far as the bifurcation of the common iliac artery. The groin wounds are sutured, but the vulval wound is so wide that it has to be left to granulate. If the vulval wound can be sutured then the cardinal principle of cancer surgery is violated and recurrence can be expected in a fair proportion of cases.

The first of these operations I performed rather in the nature of an experiment in 1941. The patient had involved nodes, and died nine years later of coronary thrombosis without recurrence of the tumour or metastases.

From 1943 onwards, with the help of my colleagues in the gynaecological and radiotherapy departments, all the cases seen in the centre were handled by me and were assessed for this radical operation; in addition, most of the cases occurring in the gynaecological departments of neighbouring hospitals, in particular the Newcastle-upon-Tyne General Hospital, were also referred. The early cases were all performed in the Royal Victoria Infirmary, but the serious bed situation created by the long stay of these patients necessitated the provision of beds specially for them, and these were provided by the Newcastle Regional Cancer Organization in their associated hospitals, where more than half of the patients described in this paper were treated. The unselfish attitude of my colleagues and the co-operation of the Regional Cancer Organization, both before and after the advent of the National Health Service, played a great part in the excellent results that have been achieved, but without the very great assistance and encouragement of Professor Harvey Evers, who was quick to see the advantages of and to encourage the establishment of a special unit for this type of case, and Mr. John Thurgar, who, in the most difficult time, handed over radiotherapy beds for the surgical treatment of these cases, this planned attack could never have been carried out.

This paper describes the results of 79 cases seen prior to March 31, 1949. A five-year follow-up is available on all these patients, and they represent an unselected group who presented themselves for treatment at Newcastle hospitals. The results are believed to be representative of what can be achieved in any large centre where these cases are concentrated in the hands of a medical and nursing staff who see enough cases to become conversant with the problems involved.

Operability Rate

The higher the operability rate of a particular surgical technique the more useful the operation becomes. Table I shows that in this series the operability rate was 83%, and

TABLE I.—Operability

Total Cases Seen	Refused Treatment	Considered Unsuitable For Radical Operation	Operated Upon
79	1	13	65 (83%)

this would appear to be reasonably satisfactory. With increasing experience—and I have now performed this operation more than 150 times—this can be increased, and were I faced with the same group of cases now I am sure that I could have successfully operated on even more of them. The causes of rejection are given in Table II. It will be noticed that most of the cases rejected because the tumour was too advanced survived only a short while, and were in most cases dying when I first saw them. It is doubtful whether I could do anything for this group even now, but cases of heart disease now present little difficulty if the operation is carried out in stages. Diabetes remains a serious problem owing to the fact that inevitable infection of the raw wound tends to make control of the diabetes exceedingly difficult. However, by staging the operation and by increasing the time interval between the stages much can be done for these patients. Age of the patient may