Alterations of theLesions of Acute Rheumatic Myocarditis during Cortisone Therapy

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The changes in the cardiac lesions of a patient dying with acute rheumatic heart disease treated with cortisone are reported. The findings indicate that the effect of this hormone upon the lesions consists in an inhibition of the inflammatory reaction without demonstrable alteration of the collagen injury.

FINAL evaluation of the therapeutic effectiveness of adrenocorticotropic hormone (ACTH) and cortisone in acute rheumatic fever must be based on alterations produced by these agents in the morphologic manifestations of the disease. We have recently observed such alterations in a patient dying with an acute exacerbation of rheumatic myocarditis who received cortisone therapy during the last 15 days of life. The changes in the acute myocardial lesions were characterized by a striking lack of inflammatory cellular response to extensive interstitial collagen degeneration. This change was confined to recent lesions; older, healing lesions appeared unaltered.

The administration of adrenocorticotropic hormone or cortisone to patients suffering from acute rheumatic fever with carditis is often associated with dramatic clinical improvement; at times it appears to be life saving. The significance of this clinical response in terms of any true alteration of the long-term course of the illness cannot as yet be ascertained. Many years of study will be required to determine if permanent damage to the heart valves and myocardium has been prevented or measurably reduced. Morphologic observations during the acute phase of illness thus assume importance and warrant detailed description.

REPORT OF CASE*

J. J., a 10 year old white female, was admitted to the Emory University Hospital on March 21, 1952.

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She had been well until September 1951, at which time she complained of stiffness and soreness of her legs not associated with joint redness or swelling. On Nov. 15, 1951, the patient complained of a sore throat. Two weeks later, she hurt her hip and two days after this noted swelling of both knees and ankles. One of the knees became red and tender. She was seen by her local physician on Dec. 1, 1951, who found her acutely ill with a temperature of 101 F., markedly dyspneic and slightly cyanotic. There was sinus tachycardia at a rate of 120 per minute with occasional extrasystoles. Two days later, cardiac dilatation and a gallop rhythm were noted. She was admitted to another hospital and was digitalized. She was placed on adrenocorticotropic hormone (ACTH), 10 mg. four times a day, for one day, and then 20 mg. twice daily until dismissal from the hospital. For several days large doses of penicillin were given. Oxygen was administered and she was sedated. She was placed on a salt free liquid diet and was given 250 cc. whole blood on two successive days. By Dec. 21, 1951, she had improved sufficiently to be discharged to home care. She was now given 25 mg. cortisone orally four times daily until Jan. 3, 1952. During the next two weeks she received 25 mg. of cortisone twice a day and for the subsequent two weeks 25 mg. per day. Cortisone was discontinued on Feb. 2, 1952. During this six weeks period she had been kept at absolute bed rest and was given .05 mg. digitoxin daily. She also received 0.6 Gm. sodium salicylate twice daily which was reduced to 0.6 Gm. daily for the following month.

On March 15, 1952, the patient became extremely dyspneic and developed severe cough. She was unable to retain food and medication. Two days later she was again hospitalized and intranasal oxygen was administered. She was placed on 25 mg. of cortisone every six hours and digitoxin was given intravenously. She was transferred to Emory University Hospital March 21, 1952.

At the time of admission to this hospital, the patient was critically ill, markedly dyspneic, pale and emaciated. Her rectal temperature was 100 F. The extremities were cool and the lips and finger tips
were cyanotic. The entire chest and body rocked with each heart beat. The cardiac apex was in the left mid-axillary line and auricular fibrillation was present, with an uncontrolled ventricular rate of 180 per minute. There was a grade 3 systolic murmur and a grade 2 diastolic rumble at the apex. A grade 1 systolic murmur was heard in the pulmonic valve area. Examination of the lungs revealed numerous coarse bubbling rales and wheezing over both lungs. The respiratory rate was 60 per minute. The blood pressure was 120/75. Femoral artery pulsations were normal and there was no peripheral edema. The liver was palpated 5 cm. below the right costal margin but the spleen was not palpable. No petechiae were found.

The red blood cell count was 4,500,000 per cubic millimeter and the blood hemoglobin content was 12.6 Gm. per 100 cc. The blood sedimentation rate (Westergren) was 50 mm. in one hour. The white blood cell count was 18,700 per cubic millimeter, with 77 per cent neutrophiles, 6 per cent band forms, 1 per cent eosinophils, 2 per cent metamyelocytes and 14 per cent lymphocytes. The specific gravity of the urine was 1.026 and the pH was 5.0. The test for sugar was 2 plus (after subcutaneous glucose with Alldase); there was no albumin. The sediment was not remarkable. A repeat urinalysis five days later showed no significant change except for I plus albuminuria and a trace of sugar. The blood Kahn test was negative. On March 22, 1952, the blood nonprotein nitrogen was 58 mg. per 100 cc. and the carbon dioxide combining power was 25 mEq. per liter. The serum chloride was 94.8 mEq. per liter and the serum sodium and potassium were 137.2 and 3.9 mEq. per liter, respectively. Four days later, the nonprotein nitrogen was 44 mg. per 100 cc., the carbon dioxide combining power was 29 mEq. per liter and the serum chloride was 95 mEq. per liter. The serum sodium and potassium were 131 and 5.0 mEq. per liter, respectively. Three blood cultures yielded no growth.

An electrocardiogram showed auricular fibrillation, with an uncontrolled ventricular rate of 160. There was moderate right axis deviation and evidence of digitalis effect. X-ray examination of the chest showed marked generalized cardiac enlargement. The diaphragmatic leaves were poorly outlined because there was fluid in both pleural cavities. There was extensive, poorly demarcated consolidation throughout both lung fields.

Course in Hospital

At the time of admission the patient was given 20 mg. of Demerol intramuscularly and nasal oxygen. She received 0.6 mg. of lanatoside C intramuscularly in an attempt to control the ventricular rate. Mercuhydrin (1 cc.) was given intramuscularly and 0.18 Gm. aminophyllin was given intravenously. Tourniquets were applied to the extremities. During the next several hours dyspnea lessened and the ventricular rate slowed to 140.

The day after admission, the patient was started on 100 mg. of cortisone intramuscularly every eight hours. This dosage was continued until the patient died, at which time she had received a total of 3,200 mg. Her temperature gradually rose, reaching 105.6 F. on the fourth hospital day. She was started on 300,000 units of procaine penicillin intramuscularly every eight hours, and 0.6 Gm. acetylsalicylic acid every four hours. Within two days the temperature had declined to 102 F. but she continued to run a low grade fever of 100 to 101 F. until death. Demerol, mercurial diuretics, aminophyllin and intramuscular lanatoside C were used in an attempt to control her congestive heart failure and severe dyspnea. Her ventricular rate remained uncontrolled. Hydration was maintained by the administration of 500 cc. of 5 per cent glucose in water at frequent intervals, with 0.5 to 1.0 Gm. of potassium chloride added on several occasions. The patient continued to have periodic episodes of pulmonary edema.

A fecal impaction became obvious on March 29, 1952, despite the fact that she had had occasional bowel movements. It was impossible manually to reach the area of impaction and frequent oil enemas were unsuccessful. The abdomen became distended and the patient became moribund. The cardiac rhythm became completely regular with a ventricular rate of 180 per minute. She died shortly thereafter, with evidence of ventricular tachycardia and fibrillation, on the eleventh hospital day.

Pathologic Findings

Autopsy was performed two and one-half hours post mortem. The body was that of a poorly nourished white girl measuring 130 cm. in length. There was slight enlargement of the right knee joint. Both pleural cavities contained 50 cc. of clear, straw colored fluid. No free fluid was present in the peritoneal cavity and there was no dependent edema.

The pericardial cavity was partially obliterated by dense, fibrous adhesions. Other areas displayed a shaggy appearance with a few loose fibrinous adhesions between visceral and parietal pericardium. No free fluid was present. The heart weighed 350 Gm. (normal weight 116 Gm.) All cardiac chambers were dilated. The mural endocardium of the left and, to a lesser degree, the right atrium appeared thickened and opaque. The valve measurements were: tricuspid valve 11.0 cm.; pulmonic valve 5.2 cm.; mitral valve 12.0 cm.; aortic valve 5.0 cm. Both cusps of the mitral valve were moderately thickened, and their chordae tendineae were shortened and frequently fused. The cusps of the tricuspid valve were slightly thickened and opaque, and there was questionable fusion of adjacent aortic valve leaflets. The pulmonic valve appeared normal. No vegetations were seen anywhere. The myo-
Fig. 1. (top left) Myocardium. A large area of recent fibrinoid degeneration in the interstitial connective tissue. Hematoxylin and phloxine \( \times 90 \).

Fig. 2. (top right) Myocardium. Acute fibrinoid degeneration of interstitial connective tissue. Note the absence of inflammatory response. Hematoxylin and phloxine \( \times 210 \).

Fig. 3. (bottom left) A myocardial Aschoff nodule of some duration. Aschoff cells and fibroblastic proliferation are present. Hematoxylin and phloxine \( \times 400 \).

Fig. 4. (bottom right) Older myocardial lesion showing almost complete fibrosis. A few Aschoff cells are still seen. Hematoxylin and phloxine \( \times 210 \).
cardium of the left ventricle measured 1.8 cm., that of the right ventricle 0.5 cm. The myocardium was flabby in consistency and pale, grayish brown in color without focal lesions.

The left lung weighed 200 Gm., the right 610 Gm. The bronchi contained a moderate amount of pink, frothy fluid. Scattered throughout both lungs were many large, confluent and ill-defined areas that were firm in consistency and appeared hemorrhagic. No thrombi were present in the branches of the pulmonary artery.

The combined weight of the adrenal glands was 9.4 Gm. There was a fecal impaction of the sigmoid colon. With the exception of passive congestion, no abnormalities were noted in the spleen, pancreas, kidneys, pelvic organs, great vessels, lymphatic tissue or bone marrow. Permission was not granted for examination of the extremities or the brain.

Tissues were fixed in Zenker's fluid with 5 per cent glacial acetic acid and in 10 per cent formalin, USP. Histologic sections were stained routinely with hematoxylin and phloxine. Selected sections were prepared with phloxine-methylene blue, Mallory's phosphotungstic acid-hematoxylin, the Gram-Weigert stain for fibrin, and the periodic acid-Schiff technique.

The myocardium revealed numerous interstitial lesions many of which were acute and of highly atypical appearance (figs. 1, 2). They consisted of varying sized, but frequently extensive and stellate areas of intense fibrinoid degeneration of collagen accompanied by little or no cellular reaction. Large mononuclear cells of the Aschoff type were completely absent, but an occasional small "myocyte" was present at the periphery of a few of these lesions. Adjacent myocardial muscle fibers appeared uninjured. This lack of cellular reaction was a striking finding in view of the large number and size of the lesions encountered.

Other myocardial lesions appeared to have been present for some time, and showed varying stages of healing (figs. 3, 4). Many revealed early proliferation of fibroblasts and contained the usual complement of large mononuclear Aschoff cells and Anitschkow myocytes (fig. 3). The oldest lesions appeared to consist of perivascular areas of dense fibrosis. None of the healing lesions appeared to differ significantly from those encountered in rheumatic myocardiitis not treated with ACTH or cortisone. The only other finding in the myocardium was a slight patchy perivascular infiltration of small lymphocytes and plasma cells and an occasional polymorphonuclear leukocyte. There was no evidence of active rheumatic arthritis.

Sections of pericardium revealed a pericarditis showing generally advanced healing. A few areas of lymphocytic and plasma cell infiltration were seen, but no acute lesions were encountered. The endocardium of the left atrium showed an extensive area of mural endocarditis in advanced repair. The mitral valve cusps contained an increase in fibrous connective tissue and were partially vascularized. Arterioles in the valve ring area demonstrated a concentric thickening and scarring of their walls. An occasional minute area of valvular endocarditis was noted near the attachment of the chordae tendineae, consisting of slight disruption of the endothelial surface and surrounding proliferation of connective tissue elements. These lesions also appeared to be of considerable standing. The tricuspid valve displayed minimal thickening by fibrous connective tissue and slight vascularization.

The lungs revealed an extensive passive congestion and patchy edema. In some areas, the alveolar septa were thickened by fibrinous tissue. Other areas showed focal fibrinous necrosis of septa with alveolar hemorrhage and fibrin deposition simulating the appearance of an asphyxial membrane. Many deposits of fibrin were undergoing organization and others were completely replaced by fibrous tissue. The recent changes in the alveolar septa were associated with a moderate interstitial infiltration of mononuclear phagocytes and lymphocytes and occasionally polymorphonuclear leukocytes. No abnormalities were noted in branches of the pulmonary arteries.

The adrenal glands revealed a marked cortical atrophy, involving principally the zona fasciculata. A moderate degree of medial cystic necrosis was encountered in the aorta. Sections of the spleen, pancreas, liver, kidneys, lymph nodes and bone marrow were not remarkable except for passive congestion.

Anatomic Diagnoses. Rheumatic heart disease, acute and chronic, with pericarditis, endocarditis and massive myocarditis; cardiac hypertrophy (350 Gm.); rheumatic pneumonitis; passive congestion of viscera; pleural effusion, bilateral; renal cortical atrophy; medial cystic necrosis of aorta; feal impaction.

Discussion

The patient, a 10 year old girl, first manifested definite clinical evidence of acute rheumatic fever in September, 1951, six months before her death. Her course indicated constant and progressive activity of her disease. Early in her illness, she was treated with prolonged courses of adrenocorticotropic hormone (ACTH) and cortisone. She received no hormone therapy for a six weeks period terminating 16 days before death. During her final hospitalization, she was given large doses (100 mg. every eight hours) of cortisone. There was no demonstrable clinical response to this therapy, and she died of intractable congestive heart failure.
The most striking finding at autopsy was a rheumatic myocarditis of atypical appearance. Acute, as well as older lesions in various stages of repair, were seen. The acute lesions consisted of extensive areas of interstitial fibrinoid degeneration of collagen, but there was remarkably little or no cellular reaction. Large mononuclear Aschoff cells were completely absent. The presence of healed and healing myocardial, valvular and epicardial lesions corresponded with the prolonged and "smoldering" clinical course. None of the older healing lesions differed significantly from those seen in rheumatic carditis not treated with adrenocorticotropic hormone or cortisone. An extensive rheumatic pneumonitis similarly revealed no alteration in cellular reaction.

Although many authors have postulated that the dramatic clinical response of acute rheumatic heart disease under adrenocorticotropic hormone or cortisone therapy is based on inhibition of the inflammatory component of cardiac lesions, morphologic observations, although few, have not supported this concept. The reports of Spain, Smith, and Rosenblum indicate no histologic alterations in the characteristic lesions of rheumatic fever. Massell and Warren noted the absence of acute cardiac lesions in a patient treated for three months for rheumatic fever with adrenocorticotropic hormone and dying with jugular thrombophlebitis.

Our findings are similar to those encountered by Bunim in subcutaneous rheumatic nodules during cortisone therapy. His text figure 8 shows a large mass of fibrinoid necrosis of collagen devoid of cellular reaction.

The lesions we have observed may be interpreted as representing a suppression of cellular reaction to altered collagen. This interpretation is in accord with the experimental observations of others, showing a quantitative inhibition by adrenocorticotropic hormone and cortisone of inflammatory cell reaction to tissue hypersensitivity reactions.

Our findings do not indicate that the injury to connective tissue associated with rheumatic fever has been prevented to any degree. Experimental observations suggest that a quantitative reduction in the number of cardiac lesions may occur during hormone administration. Bennett, Berthrong and Rich were able, in most instances, to prevent the formation of myocardial lesions associated with anaphylactic hypersensitivity in rabbits by the administration of either adrenocorticotropic hormone or cortisone. Most clinical evidence, however, indicates that acute rheumatic fever runs its natural course whether or not its manifestations are suppressed by hormone therapy.

We are unable to evaluate the effect of the morphologic alterations we have observed on the eventual fate of the lesions. Our patient received adrenocorticotropic hormone and cortisone early in her illness, but no change was apparent in the older myocardial lesions. They differed in no way from those seen in rheumatic myocarditis not treated with these hormones. Experimental observations suggest that withdrawal of hormone therapy may be quickly followed by an inflammatory cell infiltration into areas of collagen degeneration and the usual sequence of healing. Prolonged suppression of inflammatory reaction, however, might result in decreased scar tissue formation when final healing has occurred. The significance of our observations will have to be determined by the long-term studies now in progress of patients with rheumatic heart disease who have been treated successfully with adrenocorticotropic hormone and cortisone.

**Summary**

Morphologic alterations were observed in the lesions of acute rheumatic myocarditis in a patient receiving large doses of cortisone. The changes consisted of a striking lack of cellular reaction to extensive interstitial collagen degeneration. Myocardial lesions which appeared to be of longer duration displayed varying degrees of healing and did not differ from those seen in rheumatic myocarditis not treated with adrenocorticotropic hormone or cortisone.

**Sumario Español**

Los cambios en las lesiones cardiacas en un paciente que muere con una carditis reumática
tratado con cortisona se reportan. Los cambios indican que el efecto de la hormona en los tejidos consiste en una inhibición de la reacción inflamatoria sin alteración demostrable del daño colágeno.

REFERENCES

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