Combined Salicylate, Corticotropin and Corticosteroid Therapy in Acute Monocyclic Rheumatic Pancarditis

A Preliminary Report*†

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The first published accounts of the effects of corticosteroid and corticotropin on acute rheumatic carditis by Hench and co-workers in 1949-5014 precipitated an enthusiastic clinical investigation of these hormones and their analogues. An attitude of mounting optimism prevailed.3-4

In general, investigators concerned themselves with the relative merits and the toxic or untoward effects of various hormone regimens as opposed to salicylates, and related the disease response to the amount and duration of the medication administered.3-4 The treatment failures were usually proportional to the time elapsed prior to treatment.

On this idyllic scene, the joint report of the "Cooperative Clinical Trial" (1955) cast a pall of disenchantment. In a study of 497 children with acute rheumatic fever, they concluded that neither cortisone nor corticotropin was superior to aspirin, either in terms of the response of the acute disease or of residual heart damage one year later.3

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**TABLE 1—DIAGNOSTIC STUDIES**

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Note: in addition, the laboratory studies on admission included:
1. Negative urinalysis.
2. Negative V.D.R.L.
3. Normal blood glucose (122 mg. per cent 2 hours postabsorptive).
4. Negative PPD (No reaction to intermediate strength, 0.0002 mg. at 48 hrs.).
5. Negative L-E Preparation.
6. Positive throat culture for Alpha hemolytic strep.++++, Staph. albus+, N. catarrhals+ (virulence not determined).
7. Negative blood culture (no growth 2/1/60).
8. Absolute eosinophile count 56/mm³, prior to therapy.

For an explanation of this material see section of text under Diagnostic Investigation.

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This authoritative dissension created a tide of pessimism and in its wake, an explanation of this enigma was sought vociferously. One investigator postulated that rheumatic disease may vary from one section of the country to another. This thesis, however, could hardly be expected to mollify the unsettled climate of opinion within the confines of a given geographic area.

In summing up the "Current Status of Therapy in Rheumatic Fever" one year ago, the Council on Drugs of the American Medical Association made the following comments:53

"With the advent of cortisone ... hope was high that at last an agent was available which would suppress rheumatic inflammation ... However, nine years after the introduction of corticosteroid therapy ... it still cannot be stated ... whether these agents are of value in carditis or, indeed, whether they may not actually be harmful."

The question of the superiority of one form of steroid regimen or another as opposed to salicylates has long held the fascination of investigators and will probably never be resolved to everyone's satisfaction. Nevertheless, it is generally agreed each of these will suppress the manifestations of acute rheumatic fever12,16,18 and, although both corticotropin and aspirin have been employed during the withdrawal period of corticosteroids,12,18 it remains to be seen whether their effect might be additive when administered simultaneously.

We are reporting the effect of the concomitant administration of corticotropin, corticosteroids and salicylates in a patient with acute
rheumatic pancarditis. The rarity of this entity in our semi-tropical climate interdicts a statistically significant treatment experience.19,40

*Case Report*

During the second week of an illness characterized by an abrupt onset of general malaise and rapidly developing prostration, a hectic fever with daily swings from 103° to 104°F. accompanied with drenching sweats, and sharp stabbing pains in the precordium and left shoulder, Mrs. D. L., a 53 year-old Cleveland housewife, was hospitalized on January 17, 1960.

She recalled that she had had a sore throat with an acute upper respiratory infection some two weeks before the onset. Upon arriving in Florida the second day of her illness, she summoned a physician who ordered her to bed and prescribed a broad spectrum antibiotic.** The fever continued and the chest pain failed to improve.

On the fourth day, a chest x-ray film was obtained. There was striking enlargement of the heart. Compared with a routine film a year before, the transverse diameter had increased from 13 cm. to 16.7 cm. An ECG on the same day showed elevation of RST-junctions and straightening of the proximal limb of the T-waves in all leads except AVR, compatible with acute diffuse myocardial or epicardial injury.

She remained in bed and medication was continued for an additional week without improvement. After conferring with her attending physician, arrangements were made for her transfer by ambulance (some 90 miles) for hospitalization.

Transfer was uneventful. On admission, she was feverish, pale and obviously ill. Her temperature was 101.6°F. (O), 102.4°F. (R). respiration 20, pulse 100 and regular and blood pressure 100/70. The heart was markedly enlarged, but there was no discrepancy between the outer left border of cardiac dullness and the apical thrust. A grade IV pericardial friction rub was of such intensity over the precordium that the first and second heart sounds were inaudible. There was a systolic and early diastolic intensification, but the rub was not transmitted. By exploring the chest, the first and second heart sounds could be heard in the left axilla and beneath the inner third of the clavicles bilaterally. Both the hepatoljugular reflex and the Valsalva maneuver were negative. There was no cyanosis, neck vein distention, hepatomegaly, or dependent edema, and the lung fields were clear.

**PanAlba, Upjohn (tetracycline hydrochloride, 250 mg. and novobiocin sodium, 125 mg.) q.i.d.
A review of the past history and system inventory were essentially noncontributory. She said she had been told several years ago she had "a little murmur," but that "it was nothing serious."

In summary, the physical findings on admission were in keeping with a fibrinous pericarditis, with little or no serous component, and a pancarditis with diffuse cardiac dilatation.

**Diagnostic Investigation**

On the following day, the laboratory studies detailed in Table 1 were performed. The staff radiologist made a careful fluoroscopic inspection of the cardiac silhouette in multiple views with barium-filled esophagus both in the upright and recumbent positions. The following is abstracted from his interpretation: "The cardiac silhouette showed generalized enlargement.... There was no specific chamber enlargement, although the left ventricle appeared to be predominant. A spot view was taken in the posteroanterior position both supine and upright. There was no noticeable change in the cardiac silhouette. The appearance does not suggest pericardial effusion."

**Medication**

Prophylactic: Although she had received a broad spectrum antibiotic for ten days prior to admission, one million units Duracillin FA, Lilly* were administered at 72-hour intervals for a total of three injections. On the ninth day, 1.2 million units of benzathine penicillin-G were administered in a single injection and at 30-day intervals thereafter.

*Duracillin FA, Lilly (750,000 U. crystalline procaine penicillin-G and 250,000 U. buffered penicillin-G, crystalline-sodium).

**FIGURE 2:** Serial electrocardiograms show the evolving pattern (waxing and waning) of an acute diffuse myocardial and epicardial injury. The T-wave inversion was progressive (February 1, 1960) in spite of a complete reversal of the acute phase reactants, restoration of normal heart size and the disappearance of pericardial friction rub. The pattern eventually returned to normal by the fifteenth week after treatment was begun. (The ECG, one week prior to admission, showing RST-J elevation, straightening of the proximal limb and increased amplitude of the T-waves, was not available for reproduction.)
Antiphlogistic: Beginning the same day (January 18, 1960), an initial injection of 80 U. HP*ACTHAR Gel, Armour (repository corticotropin in 16 per cent gelatin) was given. Subsequently, the injections were made at 72-hour intervals with a reduction of 10 U. each injection. When the dosage reached 20 U., the injections were continued at weekly intervals for two additional weeks and the dosage was then reduced by 5 U. each week. The final injection was given during the eighth week.

Prednisone was administered concomitantly by the oral route at six-hour intervals totaling 40 mg. per day, and was maintained at this level for nine days. On the tenth day, prednisone was reduced to 2.5 mg.; and, daily thereafter on alternate doses until the total amount administered reached 20 mg. per day. At this juncture, only 1 mg. was omitted each succeeding day and by the end of four weeks the total dosage had been reduced to 2 mg. q.i.d. Medication was then reduced by a single mg. every five days. Therapy was eventually terminated after nine weeks.

In addition, 80 gr. of enteric coated aspirin were administered in divided doses daily. After two and one-half weeks this was reduced by 5 gr. daily until a level of 40 gr. was attained, which was maintained until two weeks after prednisone therapy had terminated.

Supportive: Although there was no evidence of frank congestive failure, it was felt that the persistent tachycardia and generalized cardiac enlargement portended a failing myocardium for which digitalization was justified. Digoxin was administered orally in a single dose of 1.5 mg. and was maintained at 0.5 mg. daily, later reduced to 0.25 mg. and eventually interrupted at the end of the 11th week.

To avoid sodium and water retention, 50 mg. of hydrochlorothiazide were given at breakfast daily, and to obviate potassium depletion, 1.2 grm. of potassium chloride (enteric coated) were also given daily. Both were continued throughout steroid administration, but were interrupted when the latter was discontinued.

Hospital Course

The therapeutic response was dramatic. The temperature and pulse rate returned to normal within 24 hours and remained so throughout the hospital stay. The intensity of the friction rub began to diminish by the third day and at the end of one week was no longer audible (Table 2). After the disappearance of the friction rub, the heart tones were essentially normal except for an evanescent grade I systolic apical murmur.

A recheck of cardiac size on the fourth day of therapy revealed a striking reduction of the transverse diameter of the heart to 13.8 cm. After one week of treatment, the cardiac size and contours were well within normal limits, the transverse diameter measuring 12.5 cm. (Fig. 1). The sedimentation rate had fallen from 60 mm./1 hour to 14 mm./1 hour and the hematocrit had increased from 33 vol. per cent to 41 vol.

**FIGURE 3:** A theoretical and schematic representation of the effect of the short term administration of adrenocortical hormones on the clinical course of a monocyclic attack of rheumatic fever, demonstrating escape or relapse, is overlaid on Table 2. By the prolonged administration and gradual withdrawal of both hormones and adrenocortical hormones is depicted. (Overlay from Banin, J. J.: "The Effects of Cortisone and ACTH on Rheumatic Diseases," *Bull. New York Acad. Med.*, 27:75, 1951)
per cent. The CRPA fell from 4+ to 1+, but the ASOT had increased from 125 to 166 Todd U. (Tables 1 and 2).

At the conclusion of the second week of therapy (February 1, 1960) the sedimentation rate was 3 mm./1 hour and the hematocrit 42 vol. per cent. Three days later a recheck of the CRPA was negative and the ASOT had increased to 250 Todd U. (Tables 1 and 2).

There were no untoward reactions to the medication. At no time were there any manifestations of hyperadrenocorticism, salicylate intoxication, sodium or water retention or potassium depletion. There was a gradual gain of weight of about one pound per week after the second week of therapy, which was attributed to improved nutrition.

At the time of discharge, three weeks following admission to the hospital, the only abnormalities persisting were an elevated ASOT and an abnormal ECG pattern. She was instructed to remain in bed for the first two weeks of convalescence at home (thepathetic class E), but after this, physical activities could be increased gradually at the direction of her attending physician. A therapeutic protocol (Table 2) was provided with the understanding that it was intended only as a guide, based on the assumption that her course would continue uneventful, which, happily was the case.

At the conclusion of two weeks at home, she progressed to therapeutic class D and in another two weeks, to therapeutic class C. For the next three months, she was given a free range of activity within therapeutic class B. She was then progressed to therapeutic class A.

Throughout convalescence, the sedimentation rate, hematocrit, CBC and CRPA have remained consistently normal. The ASOT, however, has never gone below 50 Todd U. The ECG pattern returned to normal 15 weeks after treatment was begun and has remained normal (Fig. 2). At the time of this report, our period of observations has been limited to six months.

CONCLUSION

1. The relative merits of aspirin, corticotropin and corticosteroids in the acute phase of rheumatic carditis has been the subject of numerous reports over the past decade, but the supremacy of any of these agents in terms of disease response has not been established.

2. It is generally agreed that any one of these agents, if administered in sufficient dosage, will suppress the manifestations of the inflammatory process of acute rheumatic fever.

3. It is postulated that a combination of these agents may have additive therapeutic value; hence, suppression of acute rheumatic activity may be accomplished with an appreciably smaller dosage of each with a consequent reduction of both toxic and untoward reactions.

4. A case of acute monocyclic rheumatic pancarditis successfully treated by the simultaneous administration of salicylates, corticotropin and corticosteroids is presented. It is believed this concept bears further exploration; however, no claim of originality is made for the treatment presented, nor is there the slightest intent to perpetuate a specific protocol.

5. Viewed in the light of our present knowledge of the natural course of rheumatic disease, and the purely suppressive role ascribed to these drugs, the rationale of inflexible, high dosage, short-term therapeutic protocols is questioned (Fig. 3).

ADDENDUM: At the conclusion of one year's observation, there is no evidence of residual heart damage.

Complete reference list will appear in the reprints.

†Deledumone 2X, Squibb (testosterone enanthate 180 mg. and estradiol valerate 8 mg. per cc. dissolved in sesame oil) was administered intramuscularly concurrently with the Bicillin at 30 day intervals as a protein anabolic agent throughout the course of steroid therapy.