Acute Myocarditis with Bundle Branch Block due to Sulfonamide Sensitivity

By Alfred Lilienfeld, M.D., Elliot Hochstein, M.D., and William Weiss, M.D.

This is a case report of a patient who developed generalized manifestations of sulfonamide sensitivity, with evidence of involvement of the skin, mucous membrane, central nervous system, liver, and myocardium. Special attention is directed to the myocardial involvement, and particularly to the development of bundle branch block. The changes were reversible and complete recovery ensued.

The clinical manifestations of sulfonamide sensitivity are well recognized. The effects on the cardiovascular system, however, have only recently been receiving the attention they deserve. The following case is presented because of the striking clinical and electrocardiographic evidence of involvement of the myocardium in association with other manifestations of sensitivity.

Case Report

The patient was a 24 year old laundress. Her past history was irrelevant. At the age of 18 she was treated for an infected finger, but a history of specific medication was not obtained. In February 1948 she developed a sore throat with fever, for which she was given sulfathiazole and sulfadiazine. Within four hours after the second dose she developed vomiting, diarrhea and abdominal cramps, and her face became swollen. These symptoms subsided in a week.

One week before she was admitted to the hospital she again developed a sore throat with fever. She was treated with sulfadiazine for five days despite the onset of abdominal cramps and diarrhea, facial edema, and confusion, immediately following the first dose. The symptoms became progressively worse and the patient was admitted to the hospital on June 14, 1948.

Examination showed a toxic, disoriented woman who was dyspneic and orthopneic. Her rectal temperature was 103.5°F. Her face was markedly swollen, and there was an erythematous, scaly rash over the bridge of her nose and over her cheeks. There were white patches on the buccal mucosa and the lingual tonsil. The soft palate was edematous. The conjunctivae were congested; the pupils and fundi were normal. The ears and nose were normal. The heart was not enlarged on percussion. The rate was rapid but regular; the sounds were distant at the apex, and the second pulmonic sound was louder than the second aortic sound. There was a presystolic gallop at the apex and a Grade 2 systolic murmur at the pulmonic area. The blood pressure was 80/70. The lungs were clear. Abdominal, rectal, and pelvic examinations revealed no abnormality. There was an equivocal Babinski reflex on the right and a positive Oppenheim reaction, and exaggerated knee jerk on the left.

On admission, the red blood cells numbered 6,000,000 per cu.mm. of blood; the hemoglobin value was 14.4 grams; there were 17,800 white blood cells per cu.mm. with 89 per cent polymorphonuclear neutrophils, of which 30 per cent were band forms; the urine was normal. A throat culture for diphtheria was negative. The blood sugar was 135 mg. per 100 cc. of blood; whole blood chlorides were 456 mg. per 100 cc.; the carbon-dioxide combining power was 56 volumes per cent; and the blood urea nitrogen was 37.8 mg. per 100 cubic centimeters. The test for sickling was negative. Serologic blood tests for syphilis were negative. The icterus index was 6.0.

Course. For the first two days the patient's condition was essentially unchanged. On the third day she went into peripheral vascular collapse, the blood pressure falling to 60/30. Five hundred cc. of plasma were administered with a rapid effect. From this time on there was a gradual improvement. The temperature, which had varied between 103.6 and 104.6 F., gradually returned to normal in two weeks. The patient became mentally alert at the end of the first week. The edema of the soft palate, the swelling of the tonsils, and the exudate on the tonsil and buccal mucosa subsided within the week. The swelling of the face and the rash disappeared by the second week. The dyspnea and orthopnea and the gallop rhythm disappeared by the end of the first week. The blood pressure rose during the second week from 100/65 to 135/100 and stabilized at 115/85.

The pathologic reflexes noted on admission were not elicited after the third day. The spinal fluid on this day showed a normal pressure; it contained 35 polymorphonuclear neutrophils per cu.mm., 82 mg.
of protein per 100 cc., and 647 mg. of chlorides per 100 cc.; the colloidal gold curve read 23333000. On the fifth day there were 5 monocytes per cu.mm. of fluid and the protein content was 121 mg. per 100 cubic centimeters. On the tenth day the protein content was 65 mg. per 100 cc. of fluid and there were no cells present. The spinal fluid Wassermann reaction was anticomplementary.

Serial hemograms showed a reduction in red blood cells to 4,000,000 per cu.mm. of blood and hemoglobin of 14 grams. The white blood cells fell from 17,800 to 10,100 per cu. mm. on the third day and varied around 5,500 thereafter on numerous counts. The differential count reverted to 70 per cent neutrophils, of which 16 per cent were band forms; there were 38 per cent lymphocytes; there were never any eosinophils present on numerous blood counts.

The erythrocyte sedimentation rate on June 23, 1948, was 10 and on July 8, 1948, it was 7 mm. per hour. Urine specimens after the initial normal findings varied in specific gravity between 1.010 and 1.020; a trace of albumin was noted in all specimens, and on two occasions only the microscopic examination showed a few white blood cells and a few hyaline and granular casts.

A blood sulfadiazine level was 6.8 mg. on the morning of the third hospital day (June 16), forty-eight hours after the last dose of the drug. On June 22, sulfadiazine was no longer present in the blood. The blood urea nitrogen fell to 14 mg. per 100 cc. on June 22. The blood serum proteins were 6.8 grams per 100 cc., with albumin value of 4 grams and globulin of 2.8 grams.

At the end of the first week (June 21) the reaction to the cephalin flocculation test was 4 + and on June 28 it was negative.

X-ray examination of the chest, performed on June 15 and June 23, by aid of the portable machine and taken with the patient in the supine position, showed no evidence of involvement of the lungs. The heart size could not be properly evaluated because of the technic employed. A 6-foot plate exposed on July 6 showed the heart to be of normal size and configuration.

Electrocardiograms made on the third day and at frequent intervals thereafter showed definite evidence of an active myocardial process (fig. 1). On June 16, there was evidence of intraventricular conduction defect with marked left-axis deviation. On June 18, the conduction defect had progressed and now assumed the pattern of a right bundle branch block. On June 23, the conduction defect had regressed, the duration of the QRS complex coming well within normal limits, but there were indications of myocardial involvement in the RS-T segments and slightly inverted T waves in Leads I and II. The T wave in Lead III was isoelectric and T waves in Leads CF, and CF, were low. On June 28 the T-wave changes in these leads were more pronounced, becoming more deeply inverted in Leads I and II, slightly inverted in Leads III and CF, and shallow and diphasic in Lead CF, The T wave in Lead CF was higher and more peaked.

On July 2, the tracing showed minimal comparative changes; the upward convexity of the RS-T segment in Lead II was less evident and the diphasic character of the T wave in Lead CF, was somewhat clearer, while the T wave in Lead CF was slightly more inverted. On July 8, the first evidences of regression were noted. The T wave in Lead I became upright, in Lead II it was less deeply inverted, in Lead CF, it was upright, and in Lead CF, it became isoelectric. On July 23, the tendency toward improvement was maintained, the T wave in Lead I becoming higher, diphasic in Lead II, lower in CF, and slightly higher in Lead CF.

On August 6, 1948, the tracing showed no essential comparative changes. The character of the T waves in Leads II, CF, and CF, however, still indicated some myocardial involvement. The patient was discharged from the hospital after four weeks' stay. A follow-up examination in the clinic four weeks later indicated that there were no symptoms, and the physical findings were normal.

**DISCUSSION**

The patient presented the clinical picture of an acute infection with marked toxicity. There was evidence of involvement of the skin, mucous membrane of the oral cavity and pharynx, the central nervous system, and the gastrointestinal and cardiovascular systems. The widespread character of this involvement suggested an etiologic factor other than the infection for which she was originally given chemotherapy. The possibility of diphtheria, scarlet fever, agranulocytosis, and pulmonary infections with sepsis which could produce such a picture was excluded on clinical and laboratory grounds. The probability of sulfonamide hypersensitivity was suggested by the history of her previous reaction in February 1948 to the administration of sulfonamides which caused immediate vomiting, abdominal cramps and diarrhea, and swelling of the face.

The criteria for the diagnosis of drug sensitivity are:

1. A history of initial use of the drug without untoward reaction. This constitutes the sensitizing dose.
2. The subsequent dose after sensitization need not be excessive, and the reaction bears no relationship to the magnitude of the dose.

...
Fig. 1: A, Sinus tachycardia, marked left-axis deviation, intraventricular conduction defect. QRS duration 0.11 second. B, Right bundle branch block, right-axis deviation, deep S1, upright QRS, and notched QRS in Lead CF. C, Disappearance of bundle branch block, QRS of 0.06 second's duration, RS-T1 and RS-T2 slightly convex upward, inversion of T waves in Leads I and II, low T waves in Leads CF and CF. D, Progression of myocardial damage, further inversion of T1 and T2, slight inversion in Leads III and CF, T shallow and diphasic in CF and higher and more peaked in CF. E, Minimal comparative changes; upward convexity of RS-T in Lead II less evident, T in CF slightly more inverted. F, First evidences of regression; T1 upright, T2 less deeply inverted, and T in CF isoelectric. G, Further regression; T1 higher, T2 diphasic, T in CF lower and less peaked, T in CF slightly higher. H, No essential comparative changes; residual T-wave abnormalities (see text).
3. The reaction does not resemble the pharmacologic or toxic effects of the drug, but assumes one of the following forms: (a) Symptoms usually associated with allergy and as such more easily recognizable, e.g., asthma, urticaria, and angioedema. (b) Symptoms resembling serum sickness. (c) Syndromes suggesting infectious disease, e.g., fever, a variety of rashes, hepatitis, agranulocytosis, thrombocytopenia; central nervous system involvement; hepatitis; and myocarditis.

4. Immunologic criteria. Antibody mechanisms are demonstrable in protein sensitization but not in the case of sensitization due to drugs of a crystalloid nature.

5. Persistence of symptoms as long as the drug is continued.

With regard to the present case, a diagnosis of drug sensitivity is postulated according to the criteria enumerated. The initial sensitization may either have occurred in 1942 at the time the patient was treated for an infected finger or may have resulted from the use of proprietary sulfonamides. Subsequent administration of but one dose of sulfonamides in February 1948 produced almost immediate acute gastrointestinal symptoms and swelling of the face. A repetition of a single dose of sulfonamides at the onset of the present illness again produced immediate gastrointestinal symptoms, followed by disorientation. Despite this, sulfadiazone was given for a week with the development of fever, rash, and mucosal involvement; the central nervous system effects were disorientation, elevated spinal fluid protein, and pathologic reflexes. A 4+ reaction to the cephalin flocculation test was indicative of involvement of the liver. The myocardial involvement which was outstanding was attested to by the dyspnea and orthopnea, gallop rhythm, accentuation of the pulmonic second sound, tachycardia, and the marked electrocardiographic changes. The bundle branch block in particular is stressed because of its rarity in the cases of sulfonamide sensitivity which have been reported.5, 6, 7

The validity of the clinical diagnosis of myocardial involvement due to sulfonamide sensitivity is supported by experimental and pathologic studies. In experimental sensitization, Rich and Gregory8 and others have shown widespread foci of parenchymatous and collagen degeneration with monocytic infiltration and arterial lesions resembling those of periarteritis nodosa. Similar lesions have been reported in patients dying during or after sulfonamide therapy. Rich and Gregory particularly emphasized the presence of the arterial lesions showing hyaline and fibrinoid degeneration of the media with perivascular infiltration of mononuclear and polymorphonuclear cells including eosinophils.

Goodman,9 in January 1948, reported a case of sulfonamide sensitivity with myocardial involvement in which a muscle biopsy showed the lesions of periarteritis nodosa.

Immunologic confirmation of the diagnosis of sulfonamide sensitivity was not obtained. This is the usual situation in the case of crystalloid drugs.

**Summary and Conclusion**

A case has been presented with evidence of reversible damage to the following: skin, mucous membrane, central nervous system, liver, and myocardium.

The history and clinical picture fulfill the criteria for the diagnosis of sulfonamide sensitivity. Immunologic studies gave normal findings as they usually do in the case of crystalloid drugs.

The involvement of the myocardium is stressed, and attention is especially directed to the unusual development of bundle branch block.

Sulfonamide sensitivity should be added to the list of causes of myocarditis, and should be considered in any case of myocarditis of obscure nature.

**References**


ACUTE MYOCARDITIS WITH BUNDLE BRANCH BLOCK

5 Frist, T. F.: Reactions to sulfonamide compounds. War Med. 5: 150, 1944.
Acute Myocarditis with Bundle Branch Block due to Sulfonamide Sensitivity

ALFRED LILIENFELD, ELLIOT HOCHSTEIN and WILLIAM WEISS

Circulation, 1950;1:1060-1064
doi: 10.1161/01.CIR.1.4.1060

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1950 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/1/4/1060

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/