Unexplained Fever and Chills Associated with Myocardial Infarction*  

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Untoward side effects of procainamide therapy have been the subject of many reports but usually with emphasis on the lupus-like syndrome. Though fever and chills have been reported, they seem to be less frequently appreciated manifestation. This report deals with two patients, both with acute myocardial infarction, who had the sudden onset of chills and fever. In each instance infection and reinfarction were excluded. In each withdrawal of the drug caused complete and permanent abatement of these signs. Because profuse diaphoresis may also be associated, and in our second case was a contributing factor to a shock-like state, the potential hazard of hypovolemia, especially in this clinical setting, is emphasized.

Untoward side effects of procainamide have been the subject of a number of reports with emphasis on the lupus-like syndrome.° Fever and chills, however, seem to be less well-recognized manifestations despite reports of a few well-documented cases.10,11

The opportunity to observe two such instances, the second of which was complicated by shock, have initiated this report.

CASE 1

A 57-year-old white man was admitted to the coronary care unit at St. Mary's Hospital in Rochester, Minnesota, with the diagnosis of acute myocardial infarction. He had sustained a cardiac arrest in the emergency room from which he was successfully resuscitated. Two weeks after admission, oral procainamide therapy, 500 mg every six hours, was initiated because of a recurrence of premature ventricular beats. One week later his temperature rose suddenly to 102°F and was accompanied by shaking chills. Infection was excluded by a complete blood count and culture, urinalysis and culture, and chest x-ray films. The possibility of a drug reaction was considered and procainamide was discontinued. Twenty-four hours later the fever and chills had completely subsided. One week later the patient's informed consent was obtained for a rechallenge with procainamide. The drug was given in a single 250-mg dose at 11 AM. His vital signs were monitored hourly. Twelve hours after the medication was administered his oral temperature rose to 103°F, preceded 1.5 hours earlier by series of chills (Fig 1). Between 11:30 AM and 12 midnight his temperature reached 104°F. By the next day at 4:30 AM (27 hours and 30 minutes from the time of rechallenging the patient with the drug), his temperature was normal and remained so. His subsequent recovery was uneventful.

CASE 2

A 49-year-old white man with a known history of atherosclerotic heart disease was admitted to the coronary care unit of FHD, Veterans Administration Hospital, Augusta, Georgia, with the diagnosis of acute myocardial infarction. Because of occasional premature ventricular beats, the patient was given oral procainamide, 500 mg every six hours. On the seventh hospital day, August 10, 1971, he was transferred from the coronary care unit to the ward.

About 6:30 AM the same day, August 10, 1971, he experienced an episode of nausea, vomiting, chills, and fever of 100.6°F. An infectious process was suspected because of past problems with urinary tract infections. Specimens of blood, urine and sputum were obtained for culture and these failed to reveal pathogenic organisms. By 9:30 AM his temperature had increased to 102°F and his blood pressure had decreased from 130/85, recorded three hours earlier, to 90/70 mm Hg. His electrocardiograms revealed a sinus tachycardia of 150 beats per minute. A recurrence of mild chest pain caused the possibility of reinfarction to be considered and the patient was readmitted to the coronary care unit. However, the

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This study was supported by an allocation from the Veterans Administration and Grant No. 69 783 from the American Heart Association.
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determinations of serum lactate dehydrogenase (LDH), serum glutamic oxaloacetic transaminase (SGOT), and hydroxyster dehydrogenase (HBD), and electrocardiograms which were obtained over the subsequent three days failed to suggest further myocardial damage. Because of unchanged LDH values, chest x-ray films and electrocardiograms, as well as the subsequent course of events, pulmonary embolism was also thought to be unlikely. He continued to sweat profusely and to remain cold and clammy in spite of an intravenous infusion of metaraminol, which maintained systolic blood pressure between 105 and 115 mm/Hg. During the night he perspired to the extent that his clothes and sheets had to be changed three times.

At 6:00 a.m. the next day, August 11, 1971, he experienced another chill with a temperature of 99°F orally, and was confused and oliguric. Because his medication included only digitalis and procainamide, it was suggested that the chill and fever might be due to procainamide so the drug was discontinued. The last dose had been given at 6:00 o'clock that morning, August 11, 1971. During the day, in spite of adequate blood pressure, the signs of a drop in cardiac output remained. An infusion of 1000 ml of 5 percent dextrose and water with 10 mEq of KCl, 32 mg of levartenol bitartrate, and 19 mg of phenolamine per liter was administered over the succeeding six hours. His central venous pressure ranged between 3 and 7 cm of water during that period. Presuming that the profuse diaphoresis over the preceding 24 hours had led to the weight loss of seven pounds, hemocoagglutination, hypotension, low central venous pressure and low blood pressure (Table 1), his physicians considered hypovolemia a significant contributing factor in the shock-like state. After an oral intake that day of 750 ml of fluid with about 2 gm of sodium chloride and after receiving an additional 750 ml of 5 percent intravenous solution of dextrose and water with 40 mEq of KCl between 9:00 P.M. and 11:00 P.M., the central venous pressure had risen to 12 cm of water.

By 7:00 a.m. the following morning, August 12, 1971, the blood pressure had risen to 110/84 and the urinal output and mentation had returned to their previous state. The norepinephrine-phenolamine support was gradually discontinued and oral rehydration was continued. The patient experienced no further chills or fever from three hours after the last dose of procainamide. His clinical condition remained satisfactory and his convalescent period was otherwise uneventful.

**Discussion**

That the fever and chills described in the first case were secondary to procainamide hypersensitivity needs no further elaboration. In the second case, the patient had such episodes without evidence of infection or reinfection, leading us to suspect that he might have a drug reaction. Withdrawal of the procainamide and subsidence of the fever and chills three hours after the last dose tended to confirm this.

Although profuse sweating has been alluded to in connection with procainamide therapy, the usual pattern has been "clamminess" in association with hypotension. The profuse diaphoresis seen in our second case contributed to the development of hypovolemia leading to the shock syndrome. Until such volume depletion was appreciated, this was particularly confusing in the context of acute myocardial infarction with its propensity for cardiogenic shock.

In a nonsensitized person, fever and chills appear within one to two weeks after the first dose, while in sensitized persons they appear within six to eight hours. The fever is remittent with the usual pattern being one or two spikes of 103° to 105° F in 24
hours. The temperature seldom returns to normal in between the spikes. The fever is frequently associated with nausea, vomiting, and chills. Upon withdrawal of the drug, rapid normalization occurs, usually within 24 to 48 hours.\textsuperscript{19}

Pierach\textsuperscript{19} summarizes the mechanisms of febrile reactions in association with drugs in general as resulting from (1) non-specific (impurities), (2) a specific chemical effect, (3) Herxheimer reaction, or (4) an allergic reaction with or without manifestations of cutaneous, vascular or gastrointestinal symptoms. In the case of procainamide, an allergic mechanism has been postulated. This may be associated with the amide group in this structure since in most of the cases reported to be allergic to procainamide, the use of the local anesthetic procaine has not been accompanied by similar allergic manifestations.

Unexplained chills and fever in patients receiving procainamide suggests the advisability of stopping the medication to evaluate its possible causative role. If profuse diaphoresis is also associated, the possibility of hypovolemia should be kept in mind. This is particularly important in the patient with an acute myocardial infarction who can ill afford a drop in ventricular filling pressure and its hemodynamic consequences.

Premonitions of Darwin's Principles

All the elements of the theory of the origin of species by means of natural selection were present in the scientific world by 1818. Buffon had suggested a variability of organic forms, and Lamarck had postulated their gradual evolution from monad to man. Buffon had seen that extinction of species was related to the struggle for survival. By 1832 there was Charles Lyell's Principles of Geology, with its exhaustive demonstration of great change by the slow workings of natural processes. In 1844 Robert Chambers' Vestiges of the Natural History of Creation appeared, offering the essence of Darwin's theory. Darwin himself admitted that his books came half out of Lyell's brain. It was the independent working out of the theory by Alfred R. Wallace that finally led to Darwin's publishing in 1859, jointly with Wallace, an abstract of the material he had been working on in secret.


\textbf{REFERENCES}