Prodromata in Acute Myocardial Infarction

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SUMMARY
One hundred patients admitted to a coronary care unit with acute myocardial infarction were interviewed from a structured questionnaire to evaluate the incidence and significance of prodromal symptoms. Prodromata occurred in 65% of the subjects; this is the highest incidence ever recorded. Chest pain was the most common symptom. Characteristically it was recurrent and progressive. Patients with prodromata in contrast to those without warning are more likely to have an anterior or anterolateral infarction and the damage is more likely to be nontransmural than transmural. Prodromata have a striking relationship to pre-existing angina. Patients with angina rarely are hospitalized for acute infarction without warning. Emotional stress was not correlated with the definitive attack of cardiac infarction but was associated with the development of prodromata in some patients. These observations suggest that acute myocardial infarction is usually the culmination of a dynamic pre-coronary process.

Additional Indexing Words:
Electrocardiography
Location of infarction
Pre-coronary state
Stress and myocardial infarction
Transmural infarction
Nontransmural infarction

Recent quickening of interest in the identification and treatment of patients with myocardial infarction prior to hospitalization emphasizes the importance of accurately categorizing a pre-coronary state. Although it is now known that some patients have multiple episodes of pain prior to clinical recognition of an acute infarct, prodromal symptoms received only sporadic mention in the clinical literature during the early part of this century. In the late 1930's, several observers called attention to the possible importance of prodromata.1, 2 Despite speculation that prodromata are frequent, however, few data concerning this important occurrence have been accumulated. Estimates of the incidence of prodromata have ranged from 15 to 50%.1-8

The present study is designed to evaluate the prevalence of prodromata in patients admitted to the hospital with a definitive diagnosis of acute myocardial infarction and to compare certain clinical findings in patients with and without historical evidence of prodromata.

Description of Study
One hundred and forty-four patients were admitted consecutively to the Coronary Care Unit of The New York Hospital during the period of study from November 1967 to July 1968. One hundred and twenty-three patients with presumed acute myocardial infarction were interviewed in detail by one of the authors within 4 to 24 hours of admission. Twenty-one patients were not interviewed for various reasons including coma, sudden death, language barrier, or a diagnosis on admission other than myocardial infarction. In 23 patients the admission diagnosis of acute myocardial infarction was not substantiated.

One hundred patients proved to have myocardial infarction and are the subjects of this study. The diagnosis of myocardial infarction was based upon appropriate history, abnormal elec-
trocardiograms, and abnormal levels of enzyme activity. In 98 of the 100 patients, careful history revealed a moment prior to hospitalization, recognized as distinct by the patient, when the definitive clinical attack of infarction was presumed to have begun. The average delay between the onset of symptoms of the definitive attack of cardiac infarction and admission to the hospital, which does not have an ambulance service, was 8.0 hours with a median value of 3.5 hours. Since the present study relates only to hospitalized patients, no information is available concerning subjects who may have died before reaching the hospital.

A prepared, standardized questionnaire was used. Frequent consultations among the interviewers insured that each subject was questioned in a similar manner. In no instance did the interview procedure interfere with management of the patient, nor were any untoward effects of the interviews observed. The patients had received sedative or narcotic medication earlier but all were considered alert at the time of interview. Twenty-five controls, consisting of patients of approximately the same mean age, hospitalized for a variety of reasons and without evidence of coronary artery disease, were also interviewed for symptoms suggesting prodromata. In this study prodromata are defined as a constellation of new symptoms of presumed cardiac origin, or worsening of existing cardiac symptoms, which precede acute myocardial infarction by a period not exceeding 2 months.

**Results of Study**

**Incidence of Prodromata**

The incidence of prodromata was extraordinarily high. Sixty-five of the 100 patients with acute myocardial infarction gave a history on detailed questioning of symptoms preceding the acute definitive episode. The average age of patients with prodromata was 60 years, compared with 64 years for patients without prodromata. One patient with prodromata was Negro; all others in the study were Caucasian.

None of the 25 control patients gave a history of prodromata.

**Analysis of Prodromata**

Pain was the dominant prodromal symptom, occurring with or without other symptoms in 59 patients (91% of those with prodromata) and absent in only six patients (9%).

In 47 patients (72% of those with prodromata) pain was the sole prodromal symptom. In 12 patients (18%) pain was associated with other symptoms. These included: dyspnea, diaphoresis, and light-headedness. In six patients (9%) pain was absent and pre-coronary symptoms included burning in the chest, dyspnea, vertigo, weakness, and fatigue.

Prodromata were recurrent in 56 patients (86%). Only nine patients (14%) had a single prodromal episode. Of the 56 patients with recurrent prodromal symptoms, 43 (77%) experienced a progressive or crescendo syndrome consisting of increasing frequency, severity, or duration of prodromal attacks before culminating in acute myocardial infarction.

The duration of the prodromal syndrome varied greatly. The shortest interval between the onset of prodromata and the occurrence of the definitive attack of acute myocardial infarction was 14 hours; the longest was 2 months. In only one patient did prodromal symptoms develop in less than 24 hours. In 10 patients (15% of those with prodromata) symptoms antedated acute infarction by 1 to 6 days; in 36 (55%) by 1 to 3 weeks; and in 18 (28%) by more than 3 weeks.

Recurrent prodromal attacks for an individual were generally similar in duration; only 12 subjects (18% of those with prodromata) experienced significant variability in duration of their prodromal attacks, while 53 (82%) had episodes of rather constant duration.

Among different patients, however, the duration of the prodromal episodes varied considerably. In 37 patients (57%), no episode exceeded 15 minutes. In 10 (15%), at least one prodromal attack lasted up to 30 minutes. Four (6%) experienced at least one attack lasting up to an hour. Fourteen (22%) had prodromal episodes of greater than 1 hour's duration.

In 41 patients (63%), prodromal episodes occurred only in relation to physical activity or emotional tension. Nineteen patients (29%) experienced prodromata only at rest. Five patients (8%) had prodromata both at rest and with activity.
In Summary

Pain was the predominant and usually the only prodromal symptom. It was commonly recurrent. Characteristically the attacks were progressive or crescendo. Duration was variable in different patients, but usually similar in a given patient.

Electrocardiographic Localization of Infarction

Analysis of the electrocardiographic location of the infarction revealed that in the total series of 100 patients, 48 had anterior or anterolateral infarctions. In 52 patients the location was “other” including diaphragmatic, 36; anterodiaphragmatic, seven; indeterminate, four; posterior, four; and subendocardial, one (fig. 1).

The location of the infarction differed significantly in patients with prodromata compared to those without prodromata (fig. 1). The infarction was anterior or anterolateral in 62% and “other” in 38% of the patients with prodromata and was anterior or anterolateral in only 23% and “other” in 77% of the patients without prodromata. This difference is highly significant (P < 0.001). Furthermore, 83% of the 48 patients in the total series with anterior or anterolateral infarctions had prodromata. Only 48% of patients with other electrocardiographic localization experienced premonitory symptoms (fig. 1). These differences are highly significant (P < 0.001).

Thus the patient with prodromata has two out of three chances of having an anterior infarction. The patient with an anterior infarction has a greater than 80% chance of having prodromata.

Angina Pectoris

A history of pre-existing angina correlated with the occurrence of prodromata. In the total series, 41% of the patients with acute myocardial infarction had a history of angina pectoris (fig. 2). Prodromata in these subjects consisted of alterations of their anginal syndromes, recognized as different by the patients, including intensification of attacks, development of new symptoms, and increased frequency and duration of anginal episodes. Of the 65 patients with prodromata, 34 (52%) had angina pectoris, while 31 (48%) did not. Of the 35 patients without prodromata, however, only seven (20%) had preexisting angina pectoris, while 28 (80%) did not (fig. 2). These differences are significant (P < 0.005). Moreover, 83% of all patients with preexisting angina pectoris had prodromata preceding acute myocardial infarction, while only 53%
Angina preceding acute myocardial infarction. (A) Incidence of angina pectoris in 100 patients with acute myocardial infarction (AMI). (B) Incidence of angina pectoris and presence or absence of prodromata. (C) Incidence of prodromata in patients with and without angina pectoris. See text for details.

Thus, preexisting angina pectoris predisposes to the occurrence of prodromata. To state the proposition another way: the patient with angina is not usually hospitalized for myocardial infarction without warning. According to our data he has a better than 80% chance of developing prodromata prior to a new infarction.

Transmural Infarction

The incidence of prodromata correlated with the extent of myocardial damage. There were 59 instances of transmural infarction as determined by the presence of pathologic Q waves on the electrocardiogram in our series (fig. 3). Of the 65 patients in the series with prodromata, 33 (51%) had transmural infarction, whereas among all the patients without prodromata, 26 (74%) had transmural infarction ($P < 0.025$) (fig. 3). Of the 59 patients with transmural infarction, 33 (56%) had prodromata. In contrast, among the 41 patients without transmural infarction, 32 (78%) had prodromata.
prodromata ($P < 0.025$) (fig. 3). Thus, prodromata are more common in patients with nontransmural infarction.

The difference in incidence of prodromata between patients with transmural and nontransmural infarctions was not due to the distribution of such infarcts between anterior and "other" locations. Our data reveal that 25 (42%) of the 59 patients with transmural infarction had anterior or anterolateral infarctions, while 34 (58%) had other electrocardiographic localization. Twenty-three (56%) of the 41 patients with nontransmural infarction had anterior or anterolateral infarctions, and 18 (44%) had other localization. These differences were not statistically significant.

**Stress and Activity Related to Prodromata and Acute Myocardial Infarction**

Of the total of 100 patients with acute myocardial infarction, 24 claimed to be subject to some sort of unusual stress during all or part of the 3 weeks prior to infarction. In 21 of these 24, the stress was predominantly emotional, involving business, personal affairs, or unrelated illness; in three it was physical. In four patients the stress occurred within 12 hours of infarction, in one patient it was between 12 and 24 hours, and in one it lasted for the full 24 hours preceding the definitive attack. In 18 patients, the unusual stress persisted for a longer time, from more than 24 hours to as long as 3 weeks before the definitive attack.

Twenty-one of the 24 patients (88%) who gave a history of unusual stress experienced prodromata while three (12%) did not. Of all patients with prodromata, 21 (32%) reported pre-infarction stress, compared to only three (8.5%) of patients without prodromata. These differences were significant ($P < 0.02$).

There was no significant difference between patients with and without prodromata with regard to activity at the time of the definitive attack of infarction. Twenty-three patients were either asleep or resting in bed, 70 were engaged in usual activity, and five were engaged in unusual activity. Two patients did not have a clearly definable clinical onset for the infarction.

**Associated Pathophysiologic Conditions**

Of various other conditions associated with coronary artery disease, we considered as significant a definitive history, or evidence of diabetes mellitus, hypertension, peripheral vascular disease, or hypercholesterolemia. Thirty-three per cent of the patients in our total series had one or more of these conditions. In this group of 33 patients, the incidence of prodromata was 79% (26 patients), compared to an incidence of 58% (39 patients) in the 67 patients without one or more associated conditions ($P < 0.05$). One or more of these conditions occurred in 40% (26 patients) of those with prodromata. They were found in only 20% (seven patients) of those without prodromata ($P < 0.025$).

**Sex Distribution**

In the total series there were 76 males and 24 females. Among the males, the incidence of prodromata was 70%. It was 50% among female patients.

Of all patients with prodromata, 53 (82%) were male and 12 (18%) female. Of the patients without prodromata, 23 (66%) were male and 12 (34%) female ($P < 0.05$).

**Other Factors**

Analysis of the location and duration of symptoms of the definitive attack of acute myocardial infarction revealed no differences among patients with and those without prodromata. The frequencies of previous myocardial infarction, family history of cardiovascular disease, and history of smoking were similar among those with prodromal symptoms and those without.

Analysis of the hospital course failed to demonstrate significant differences in the incidence of heart failure, arrhythmia, shock, or mortality rate between the patients with and those without prodromata.

**Discussion**

The present study, based on an analysis of symptoms recalled shortly after hospitalization by 100 patients with proven myocardial infarction admitted to a coronary care unit, has revealed that two of three subjects had a clear-
cut warning before the apparent definitive attack. This, to our knowledge, is the highest incidence ever recorded. It may be lower than actually present since denial is such a strong component of the defense mechanism when a patient is faced with acute illness.

The data also demonstrate that a discrete moment as the clinical onset of acute infarction can usually be identified from a careful review of the medical history. Furthermore, the recurrent, progressive symptoms which characterize prodromata were distinguished by the patients from their pre-existing angina. Identifying a discrete period as the clinical onset of an illness does not, of course, necessarily imply understanding of the pathophysiologic event. Information is not available to determine whether the clinical onset of myocardial infarction in man represents the moment when pathologic, metabolic, or electrocardiographic changes occur.

While provocative, the present observations apply only to a circumscribed sample of the population at risk for myocardial infarction. This study encompasses only patients who survived to be admitted to a teaching hospital which lacks an ambulance service. It is now recognized that more than 50% of patients with acute myocardial infarction do not survive to reach a hospital. Further inquiries are needed to determine whether our findings are applicable to the general population at risk for myocardial infarction.

The present study provides no information regarding the incidence of subsequent cardiac infarction in all patients who develop prodromata. We have no data on patients who develop a prodromal syndrome but do not progress to clinical infarction. In view of the striking association between angina pectoris and prodromata, it would be useful to study a population with angina to determine the incidence of prodromata or change in patterns of angina. Since the majority of instances of sudden death probably represent an expression of coronary artery disease, it would be important to determine whether patients who die suddenly have had prodromata. Obviously, further data from prospective studies of high-risk populations are necessary before the significance of the prodromal syndrome can be fully realized.

Feil, in 1937, reported that in approximately 50% of patients with acute myocardial infarction the attack is preceded by premonitory chest pain. Sampson and Eliaser recorded the incidence of prodromata to be 48%. Maurice and associates noted that 39% of patients with myocardial infarction have symptoms from several hours to a month or more before the definitive attack. Wood stated that 45% of individuals with acute myocardial infarction had prodromal symptoms. Mounsey reported the incidence to be 29%. Vakil recognized premonitory symptoms in 39% of patients. Behrmann and co-workers stated that 16% of acute infarctions were preceded by premonitory warning. Yater's group found that 10% of men under 40 years of age with myocardial infarction had prodromal symptoms within 3 weeks of the infarction and that 49% had some symptoms which preceded infarction by more than 3 weeks.

Many factors may account for the wide range of incidence of prodromata reported in acute myocardial infarction, including errors inherent in drawing conclusions from small groups of patients, variability in diagnostic criteria, and sampling from different populations. Most likely, however, the differences are a reflection of the methods of study. Most of the earlier data were derived from retrospective analysis of records transcribed by a variety of observers who were not aware of, or seeking specific information concerning prodromata. In our own study, many instances were encountered in which an unequivocal history of prodromata was obtained, but this information had not been elicited by the admitting physician.

Chest pain is by far the most common prodromal symptom. We found, unlike prior authors, that the pain in most instances appears rather typical of ischemic cardiac pain, being described usually as squeezing, tightening, pressure, or heaviness in the chest. Unusual pain syndromes were uncommon. Prodromata to acute cardiac infarction are
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generally repetitive and progressive or crescendo. This dynamic aspect has been noted only once previously.5

The correlation between anterior or antero-lateral infarction and prodromata has not previously been recognized. Among the 11 patients with prodromata reported by Feil,1 in whom electrocardiographic localization of the infarct was possible, eight had anterior or antero-apical infarctions. The significance of the relationship between prodromata and the location of infarction is not entirely clear, but differences in the pattern of blood flow in vessels supplying various parts of the myocardium may provide an explanation. In posterior or diaphragmatic infarctions, areas usually served by branches from the right coronary artery,10, 11 prodromata are uncommon. Anterior and antero-lateral infarctions generally reflect involvement of the anterior descending coronary artery.12

The pattern of blood flow in the left and right coronary arterial systems is different,13, 14 and flow per gram of myocardium in the right coronary artery is about one half that in the left.15 Many factors may account for variations in coronary blood flow, including the more extensive branching of the left coronary system, angulation of the left anterior descending artery during systole, higher tension in the left ventricle than in the right, and the tendency for more severe obstruction to occur in the left coronary system.16

The possibility that the postero-diaphragmatic surface of the heart is less sensitive to pain than the anterior surface should be considered as an alternative explanation for the relationship between the electrocardiogram and prodromata. Yanowitz and associates17 have shown that although sympathetic innervation of the ventricles from the right and left stellate ganglia overlap, the influence of the left stellate ganglion is predominant over the posterior wall of the ventricles, while right stellate influence dominates the anterior ventricular walls. Whether sensory innervation is similarly divided is unknown, and whether alternations in sensory nerve tone indeed exist, as have been postulated for the sympathetic responses of the individual stellate ganglion, is purely speculative.

The importance of stress or unusual exertion in cardiac infarction is controversial. While most of the subjects commented that they were normally under stress in their daily lives, the present study suggests that events perceived as unusually stressful are more common in patients who have prodromata than in those who do not. We have no information to evaluate the question whether patients who reported increasing stress and prodromata were indeed subjected to greater forces than usual or rather had changes in their perception of what was stressful.

Emotional stress or unusual activity could not be related to the definitive clinical episode of acute cardiac infarction in our series. Twenty-three per cent of the patients were in bed, 70% were engaged in usual activity, and only 5% were participating in unusual activity at the time of the infarction. The low incidence of stress at the time of the acute attack is similar to the finding of Master and associates18 but is in contrast to the observations of others8, 19 who have noted a significant relationship between unusual activity and acute infarction.

The overall incidence of angina pectoris in our series, 41%, is comparable to earlier reports.20 Eighty-three per cent of all patients with pre-existing angina in our series had prodromata. In contrast in patients without angina the incidence of sudden infarction without prodromata was approximately equal to that of infarction preceded by prodromata. The implication is clear: change in the pattern of established angina should be viewed with grave suspicion. Changes recognized by the patient consist of increased frequency, severity or duration of pain episodes, or development of new symptoms.

Patients with angina pectoris usually have diffuse coronary artery disease. The striking association between angina and prodromata suggests that circulatory factors may be important in the development of the latter. Presumably prodromata are manifestations of hypoxia. Hypoxia is a major stimulus for the
development of collateral coronary circulation. Extensive collaterals may limit the extent of ventricular necrosis when infarction occurs. Our data indicate that patients without prodroma more commonly have transmural infarction. Such lesions may well be larger than the nontransmural infarcts more likely to occur in the patient with prodroma. The finding of Miller and associates that transmural infarction is five times more common in cases of acute coronary artery occlusion than in cases in which there is a prior syndrome of coronary insufficiency supports this thesis. These observations suggest the need for more precise clinicopathologic correlation related to the pre-infarction state.

When prodroma to myocardial infarction emerge, it is likely that circulation to the myocardium is gradually being compromised, or the work of the heart episodically exceeds the available oxygen supply, or both. A significant rise in blood pressure during spontaneous and exertional angina pectoris is now well recognized. Modest pulse rate increases have also been observed in our laboratory. The result is a significant increase in cardiac pressure-work per minute. Alterations during emotional stress may also result in increased myocardial oxygen requirement. If the patient with gradually progressive coronary artery disease has an exaggerated pressor response to his ischemic pain, the stage may be set for a crescendo cycle of ischemia, pain, pressure rise, more ischemia expressed as prodroma, and finally acute infarction. We suggest, therefore, that the emergence of prodromata represents a dynamic interplay between changes in the coronary and systemic circulation. Appropriate therapy for the impending coronary syndrome must be based on improved understanding of the pathophysiology of prodromata.

References

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Galahads in Science

. . . scientists are “problem-seekers.” Unlike most of the rest of mankind, who regard problems as something to be avoided, the scientist goes out and looks for them. If he cannot manage things so that his life is an endless succession of problems, he counts himself a failure. . . . Most men throughout history have spent their lives desperately trying to solve problems they did not seek out, and failure to solve those problems has all too often meant trouble and tragedy. It is hardly surprising that men have come to think of happiness as the absence of problems. . . .—John W. Gardner: No Easy Victories, edited by Helen Rowan. New York, Harper & Row, 1968, p. 31.
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