Myocardial Infarction in Younger Women*
Associated Clinical Features and Relationship to Use of Oral Contraceptive Drugs

Federico G. Arthes, M.D.,** and Alfonse T. Masi, M.D.†

In a study of thromboembolism and oral contraceptive drugs, 136 cases of myocardial infarction in women aged 30 to 44 years were identified, a rare disease in women of this age group. Data from their hospital medical records were compared with those of several other groups, including women without chronic disease admitted for various acute or elective conditions unrelated to thromboembolism, patients with thromboembolic disease other than myocardial infarction, and women queried or examined in the National Health Survey. The following attributes were found to be associated with myocardial infarction in younger women: presence of diabetes; hypertension; history of increased cigarette smoking; and hypercholesterolemia. A history of the use of oral contraceptive drugs was found with greater frequency in cases than in controls. The literature on the possible association of myocardial infarction and the use of oral contraceptives was reviewed.

Women below the age of 45 years seldom have a myocardial infarction. Of 6,954 patients hospitalized for myocardial infarction during a four-year period comparable to this study (1966 through 1969), less than 1 percent (56 patients) were female subjects under 45 years of age. Over a six-year period in the Framingham study group, the average annual incidence of coronary heart disease evidenced by myocardial infarction, angina pectoris, coronary insufficiency, or death due to coronary heart disease was only 0.3 per 1,000 women between the ages of 30 and 44 years, contrasted to 2.5 per 1,000 men. Similarly, in New York state (exclusive of New York City) the death rate from arteriosclerotic heart disease, including coronary arterial disease, was less than 0.1 per 1,000 women between the ages of 25 and 44 years during the period of 1959 to 1960. Regarding clinical studies, of 53 young patients (aged 40 years or younger) with myocardial infarction, only two were women; the youngest patient was a 21-year-old woman with severe juvenile diabetes mellitus, and the other woman was 36 years old and without known predisposing factors. Weinreb et al found only five women under the age of 40 years among a series of 219 female patients with myocardial infarction, and James et al found only five women under the age of 40 years among their series of 146 women with myocardial infarction. Finally, in an earlier study of over 95,000 women less than 40 years of age admitted to the Mayo Clinic (1935 to 1945), only seven had a definite diagnosis of myocardial infarction.

As a consequence of the rarity of myocardial infarction in younger women, most information on the disease is based on studies of men and older women. Relatively little is known about characteristics associated with myocardial infarction in younger women. A previous study of thromboembolism in relation to the use of oral contraceptive drugs afforded the opportunity to investigate a large series of younger women with myocardial infarction that were included in that survey. In the group aged 30 to 44 years, 136 cases of myocardial infarction were identified, and the data from these hospital records were compared to those of several other groups, including women without chronic disease admitted to the same hospitals for conditions unrelated to thromboembolism, women admitted for various....

*From the Department of Epidemiology, School of Hygiene and Public Health, the Johns Hopkins University, Baltimore, and the Division of Connective Tissue Diseases, Department of Medicine, University of Tennessee Center for the Health Sciences, Memphis. The data in this analysis were derived from a previous study supported by contract 67-10 from the Food and Drug Administration, Department of Health, Education, and Welfare, and this work was supported in part by grants AM 12049 and AM 05055 from the National Institute of Arthritis, Metabolism, and Digestive Diseases.

**Assistant Professor of Epidemiology, Baltimore.

†Professor of Medicine and Director, Division of Connective Tissue Diseases, Memphis.

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Reprint requests: Dr. Masi, 855 Madison, Memphis 38163

574 ARTHES, MAS
types of thromboembolism other than myocardial infarction, and women queried or examined in the National Health Survey. The aim of this report is to describe certain features that were found to be associated with myocardial infarction in younger women and to evaluate its possible relationship to the use of oral contraceptive drugs.

**Materials and Methods**

**Group with Myocardial Infarction**

During the interval of 1966 to 1969, the Johns Hopkins Cooperating Hospitals' Study of Idiopathic Thromboembolic Diseases was conducted in women of child-bearing age. Its primary purpose was to investigate the relationship of idiopathic thromboembolism to the use of oral contraceptive drugs; and these results were published separately.8 A secondary purpose was to analyze other clinical and epidemiologic features of the total group of patients, and this study describes findings related to those with acute coronary occlusion and myocardial infarction.

Details on the 47 hospitals included in the parent study and on the methods of case selection are described in the previous report; briefly, however, the 47 hospitals located in five cities in the eastern United States included 21 primary and 11 major-affiliation institutions of 16 medical schools, plus 15 hospitals with medical-school affiliation. Records of female patients between the ages of 15 and 44 years who had been admitted between 1964 and 1968 with any thromboembolic disorder, including myocardial infarction, were reviewed. Data from 2,884 hospital medical records of such patients with thromboembolism were abstracted on a detailed standard form by hospital residents, supervised and aided by members of the investigative team. After review of these patients' abstracts, 140 were accepted as having acute myocardial infarction; all cases had a discharge diagnosis of acute myocardial infarction (indexed as 420.1, International Classification of Diseases, adopted [ICDA] 1960 revision) based on consistent historical, physical, or pathologic findings plus typical serial changes in either electrocardiograms or serum levels of enzymes. No cases had evidence either of secondary coronary occlusion (eg, systemic vasculitis, septic or prothrombotic valvular embolization) or of nonmalignant causes of increased serum enzyme levels. This sample does not include patients who either were admitted to the hospital deceased or who did not survive long enough to have a medical history, physical examination, and initial laboratory evaluation completed.

As only four of the patients with myocardial infarction were under 30 years of age, they were excluded, and analyses in this report are limited to the 136 women aged 30 to 44 years old in whom the diagnosis of myocardial infarction could be supported. Initial ECGs on 126 patients showed abnormalities consistent with myocardial infarction; eight were considered normal, and two were unavailable. From 128 patients, serial tracings were obtained, of which only three ECGs were considered to be negative for myocardial infarction by the hospital cardiologist; but the clinicalcourse and other findings supported the diagnosis in these three patients. There were no significant clinical cardiovascular complications in 101 of the cases; of the remaining 35 cases, 22 showed congestive heart failure, eight showed arrhythmias, and five had cyanosis. Chest x-ray films were available from 102 cases and revealed no evidence of cardiac enlargement in 72 patients; ten patients had left ventricular enlargement, 19 had generalized cardiomegaly, and one had mitral heart configuration. Levels of serum glutamic oxaloacetic transaminase (SGOT) were analyzed in 124 patients; 66 showed significant changes on serial examinations, and 44 did not show significant serial changes, but only nine patients had a value of 40 units/ml or less. Nearly half of the patients had a history of angina, but only 9 percent had had a previously diagnosed myocardial infarction. Eleven percent died, which is similar to the mortality of 13 percent in female patients under the age of 60 years who were hospitalized with myocardial infarction in a large community study. From the available evidence, including clinical history, ECG, SGOT level, and chest x-ray film, the diagnosis of myocardial infarction is considered to have been adequately supported in all patients accepted in this study.

**Comparison Groups**

To be considered "idiopathic" in the previous study, a case of thromboembolism, including myocardial infarction, would have had to be a patient suffering from the first attack of the disease who was free from previous manifestations, (eg, angina) and from other significant chronic disease (such as diabetes or hypertension). No patient with myocardial infarction was found who met all of these rigid criteria, although no special attempt was made to exclude patients with myocardial infarction from the idiopathic category. Thus, none of the previously identified idiopathic cases of thromboembolism included patients with myocardial infarction. No controls were chosen for the patients with myocardial infarction, and no patients with myocardial infarction were interviewed, as were the idiopathic cases and their matched "healthy" controls without chronic disease analyzed in the previous study.

Although no matched control group was selected for the patients with myocardial infarction, their large number, abstracted in considerable clinical detail and in a standard fashion, stimulated this comparison with the other available patients from 30 to 44 years similarly reviewed in that study.

One such comparison group consists of women without chronic disease selected to match the idiopathic thromboembolism cases. They were included in the original study mainly for comparison of prior history of use of oral contraceptives and because of preselection, are not valid controls in this study for comparison of preexisting medical conditions. This comparison group consisted of women mainly admitted for acute illnesses, without any thromboembolic manifestations, and free of any significant chronic disease or predispositions, as were the patients with idiopathic thromboembolism. These "healthy" patients were matched on a large number of factors with the idiopathic cases of thromboembolism. Some patients were interviewed in their homes, and some were not. The data from the interviews were not utilized in the present study. This group will hereafter be referred to simply as "controls." There were 254 such patients aged 30 to 44 years.

A second comparison group consisted of 1,391 women aged 30 to 44 years who had thromboembolic disorders other than myocardial infarction. This group included cases of peripheral thrombophlebitis, pulmonary embolism, cerebral thrombosis, and other less frequent thromboembolic diseases. The women were subdivided into three classes, as follows: (a) 135 patients with idiopathic thromboembolic diseases other than myocardial infarction; (b) 407 patients with thromboembolism following surgery or trauma; and (c) 849 patients with thromboembolism associated with a medical condition believed to be predisposing to or precipitating of thrombo-
embolism, as specified in the previous study, without regard to oral contraceptive usage. The data secured from medical abstracts of these groups were compared with those from the patients with myocardial infarction in this series, after adjustment for residual differences in age and other characteristics when necessary. Some comparisons were also made with data from the National Health Survey for women of the same ages. Adjustment for age differences was done by the direct method using a standard population of 100 subjects in each five-year age class.

RESULTS

The percentage by race and age of patients within the various diagnostic groups is given in Table 1. Patients with myocardial infarction were older as a group than those in other categories. Over two-thirds were aged 40 to 44 years, markedly exceeding any of the comparison groups (P < 0.001), and probably a valid difference from other categories of thromboembolism, since no selection was made by age. The age difference was taken into account by age adjustments in comparing the prevalence of risk factors between groups. Differences by race were small. The marital status, religious preference, and hospital pay status were compared between the groups, and no important differences were seen when allowance was made for age.

Table 2 compares the smoking habits of patients with myocardial infarction and the various others who had such information specified in their charts. Comparison is made on the basis of expected numbers of women in each diagnostic group and smoking category, with expected numbers being derived from marginal totals and, hence, heavily weighted by medically predisposed cases of thromboembolism. A comparison was also made on the basis of the relative risk of heavy smokers observed in each group compared to controls. Frequencies adjusted for age and race did not alter the findings.

The number of nonsmokers is below expectation for patients with myocardial infarction, controls, and patients with idiopathic thromboembolism; heavy

### Table 1—Race and Age Distribution (in Percentages) of Diagnostic Groups

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>White</th>
<th>Nonwhite</th>
<th>All Races</th>
<th>Total No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>6</td>
<td>18</td>
<td>51</td>
<td>1</td>
</tr>
<tr>
<td>Controls for idiopathic thromboembolism</td>
<td>30</td>
<td>25</td>
<td>28</td>
<td>7</td>
</tr>
<tr>
<td>Idiopathic thromboembolism</td>
<td>20</td>
<td>23</td>
<td>27</td>
<td>12</td>
</tr>
<tr>
<td>Thromboembolism precipitated by trauma or surgery</td>
<td>17</td>
<td>28</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>Thromboembolism with medical predisposition</td>
<td>14</td>
<td>22</td>
<td>34</td>
<td>7</td>
</tr>
</tbody>
</table>

### Table 2—Smoking Habits of Patients by Diagnostic Groups

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>Smoking Habit Stated, No. (Percent)</th>
<th>Non smokers</th>
<th>Occasional-Light</th>
<th>Moderate</th>
<th>Heavy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>Expected</td>
<td>Observed</td>
<td>Expected</td>
<td>Observed</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>98 (72)</td>
<td>31</td>
<td>40.2</td>
<td>15</td>
<td>19.4</td>
</tr>
<tr>
<td>Controls for idiopathic thromboembolism</td>
<td>128 (50)</td>
<td>45</td>
<td>52.5</td>
<td>24</td>
<td>25.3</td>
</tr>
<tr>
<td>Idiopathic thromboembolism</td>
<td>93 (69)</td>
<td>32</td>
<td>38.2</td>
<td>18</td>
<td>18.4</td>
</tr>
<tr>
<td>Thromboembolism precipitated by trauma or surgery</td>
<td>212 (52)</td>
<td>92</td>
<td>87.0</td>
<td>51</td>
<td>41.9</td>
</tr>
<tr>
<td>Thromboembolism with medical predisposition</td>
<td>522 (62)</td>
<td>232</td>
<td>214.2</td>
<td>100</td>
<td>103.1</td>
</tr>
</tbody>
</table>

*χ² = 27.30; P < .01.

**Current use of cigarettes was classified as follows: occasional-light, does not smoke daily or less than 10 cigarettes daily; moderate, 10 to 20 cigarettes daily; and heavy, 21 or more cigarettes daily. Expected frequencies were derived from marginal totals, limiting analysis to those whose smoking status was known.

†Relative risk of heavy smokers observed in each group, compared to controls for idiopathic thromboembolism, is shown in parentheses; the only significant difference found was with myocardial infarction (P < 0.05).
All smokers (more than one pack daily) are substantially in excess only for patients with myocardial infarction, with a relative risk of 2.2. For moderate (one-half to one pack daily) and heavy smokers combined, the observed number of cases of myocardial infarction is 52; the expected number was 38.4. Since no category of patients was selected on the basis of prior smoking history, a statistical comparison may be made among all groups. Regarding heavy smoking, a significant difference was found among groups (P < 0.02); the major excess was derived from the patients with myocardial infarction. Also, their frequency of heavy smoking was significantly greater than that of other medically predisposed patients with thromboembolism (P < 0.02).

Table 3 compares the patients with myocardial infarction whose smoking history was recorded with smoking histories from the National Health Survey of women aged 25 to 44 years.9 The smoking frequencies shown are based on the current smoking habits of the groups. The patients with myocardial infarction have a greater proportion of all smokers and persons smoking more than one pack per day, which would not be expected by chance (P < 0.001).

The mean admission blood pressure levels of the 101 patients with myocardial infarction but without overt cardiovascular complications were compared to the levels of women examined in the National Health Survey. Twenty-nine patients with myocardial infarction and with a history of hypertension (as specified in the medical record) had a mean systolic pressure of 147.9 mm Hg and a mean diastolic of 95.9 mm Hg. These means are much higher than those for the subgroup of 72 cases without a history of hypertension (126.7 mm Hg systolic and 82.7 mm Hg diastolic). Ambulatory women aged 35 to 44 years examined in the National Health Survey10 had a mean systolic blood pressure of 122.8 mm Hg and a diastolic pressure of 78.0 mm Hg. Thus, in the group with myocardial infarction, a large proportion (29 percent) had a history of hypertension with admission blood pressures considerably higher than expected from National Health Survey data. The remaining patients without such a history still showed a slightly higher mean level of blood pressure than expected in the general population. Since blood pressures measured at admission often do not reflect preexistent levels, one cannot quantitate the degree or proportion of excess hypertension among patients with myocardial infarction from these data, and the possibility of bias resulting from exclusion of the 35 cases with overt complications cannot be excluded. Nevertheless, all factors considered, the data on blood pressures measured at admission suggest a significant excess of preexistent hypertension.

Table 3—Current Cigarette Smoking Status of 98 Patients with Myocardial Infarction

<table>
<thead>
<tr>
<th>No. of</th>
<th>No. of</th>
</tr>
</thead>
<tbody>
<tr>
<td>cigarettes daily among all smokers (67):</td>
<td>Expected*</td>
</tr>
<tr>
<td>10 or fewer</td>
<td>15</td>
</tr>
<tr>
<td>11 to 20</td>
<td>30</td>
</tr>
<tr>
<td>21 to 40</td>
<td>20</td>
</tr>
<tr>
<td>Over 40</td>
<td>2</td>
</tr>
</tbody>
</table>

*Expected number based upon smoking habits of women aged 25 to 44 years in National Health Survey.

smokers (more than one pack daily) are substantially in excess only for patients with myocardial infarction, with a relative risk of 2.2. For moderate (one-half to one pack daily) and heavy smokers combined, the observed number of cases of myocardial infarction is 52; the expected number was 38.4. Comparable figures for the controls are 59 and 50.2; and for all categories of thromboembolism, excluding myocardial infarction, the figures are 302 and 324.4. Since no category of patients was selected on the basis of prior smoking history, a statistical comparison may be made among all groups. Regarding heavy smoking, a significant difference was found among groups (P < 0.02); the major excess was derived from the patients with myocardial infarction. Also, their frequency of heavy smoking was significantly greater than that of other medically predisposed patients with thromboembolism (P < 0.02).

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Table 4—Serum Cholesterol Level for Patients with Myocardial Infarction, Other Diagnostic Groups, and Women in National Health Survey

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>No. of Determinations (Percent)</th>
<th>Mean Serum Cholesterol, mg/100 ml</th>
<th>Percent Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;160 mg/100 ml</td>
<td>160-239 mg/100 ml</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>88 (65)</td>
<td>251.8 ± 66.0</td>
<td>5.1</td>
</tr>
<tr>
<td>Controls for idiopathic thromboembolism</td>
<td>17 (7)</td>
<td>220.0 ± 58.3</td>
<td>11.8</td>
</tr>
<tr>
<td>Idiopathic thromboembolism</td>
<td>30 (22)</td>
<td>228.0 ± 69.2</td>
<td>23.3</td>
</tr>
<tr>
<td>Thromboembolism precipitated by trauma or surgery</td>
<td>66 (16)</td>
<td>212.1 ± 58.8</td>
<td>19.7</td>
</tr>
<tr>
<td>Thromboembolism with medical predisposition</td>
<td>235 (28)</td>
<td>220.2 ± 58.8</td>
<td>14.9</td>
</tr>
<tr>
<td>National Health Survey*</td>
<td>213.6 ± 45.3</td>
<td>6.5</td>
<td>67.0</td>
</tr>
</tbody>
</table>

*Women aged 35 to 44 years.
among women having myocardial infarction compared with the population in general.

Serum cholesterol levels were determined in two-thirds of the patients and are shown in Table 4, along with the other subclasses of patients with thromboembolism, the controls, and the National Health Survey subjects.\(^{11}\) There is considerable difference between laboratories and techniques for cholesterol determinations. This factor is likely to affect mainly the comparison between the hospitalized patients and the National Health Survey data, since the latter determinations were made in a single laboratory, while the five groups of hospitalized patients had their determinations made in various hospitals. Cholesterol levels were not considered in classifying patients in this study. We realize that the data on patients are incomplete, but the data are offered as a crude comparison. The patients with myocardial infarction had the highest mean cholesterol level and the highest proportion with values over 320 mg/100 ml. The modest relationship requires confirmation in a more carefully controlled analysis.

Only five medical records from cases of myocardial infarction lacked a statement in regard to diabetes. Of the 131 with a definite statement, 29 patients (22 percent) had a clinical diagnosis of diabetes. According to the National Health Survey,\(^{12}\) only 0.62 percent of women aged 25 to 44 years have this diagnosis. The comparison groups of women of the same age with thromboembolic disease also show a high percentage of diabetes, although much less than the patients with myocardial infarction (Table 4). The differences persist after adjustment for age.

Of the 136 patients with myocardial infarction, 43 had no statement concerning their menstrual history in their records. Among the 93 whose menstrual history was recorded, 28 had a surgically induced menopause more than six months before the current illness, leaving 65 patients who were still menstruating. No patient with myocardial infarction had had a natural menopause prior to her admission, according to the records available.

Age-adjusted percentages for use of oral contraceptive drugs among the groups of patients (excluding patients with menopause) were as follows: patients with myocardial infarction, 19 percent; controls, 7 percent; patients with idiopathic thromboembolism, 35 percent; patients with postsurgical and trauma-related thromboembolism, 14 percent; and patients with medically predisposed thromboembolism, 20 percent. The proportion observed among controls (7 percent) is close to the 9.8 percent expected on the basis of the age-specific proportions for use of oral contraceptives in a national sample of married women interviewed in 1965.\(^{13}\)

The most appropriate comparison with respect to the use of oral contraceptives is with the group selected as controls for the idiopathic cases of thromboembolism. This is because both idiopathic and postsurgical thromboembolism have been shown to be associated with the use of oral contraceptives.\(^ {14-22}\) Comparison is of necessity limited to those 65 individuals whose medical history indicates that the patient was still menstruating. Adjustment for age differences is essential because the two series differ widely on age, and contraceptive practices are highly age-dependent. The variance of the difference for each age class was estimated by the method given by Mantel and Haenszel.\(^ {23}\) The total observed number of users of oral contraceptives among the 65 menstruating patients with myocardial infarction was eight, and the expected number is 4.7. With correction for continuity, \(z = 1.7,\) and, thus, the difference was not significant at the probability level of 0.05; however, in the group aged 35 to 39 years alone, there is a significantly higher frequency (\(P < 0.02\)) of use of oral contraceptives by patients with myocardial infarction (five of 15) than by this control group (two of 34).

**Table 5—Presence and Therapy of Diabetes in Diagnostic Groups of Thromboembolic Disease**

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>Patients with Information Available</th>
<th>Diabetes Present</th>
<th>Therapy for Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Untreated or Uncontrolled</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>131 (96)</td>
<td>29 (22)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Thromboembolism precipitated by trauma or surgery</td>
<td>374 (92)</td>
<td>16 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Medically predisposed thromboembolism</td>
<td>798 (94)</td>
<td>62 (8)</td>
<td>8 (13)</td>
</tr>
</tbody>
</table>

*Table values are numbers of patients; numbers within parentheses are percentages.
**Receiving either oral hypoglycemic agents or less than 30 units of insulin daily.
DISCUSSION

Information on personal characteristics, such as race, sex, religion, and marital status, was practically always found in the medical records; however, some personal attributes, such as smoking habits, menstrual history, and weight status, were recorded in varying degrees of completeness depending on the hospital service of admission and possibly on the importance of the attribute to the reason for admission.

For example, a history with regard to smoking was found in 72 percent of the medical records from the patients with myocardial infarction but in only one-half of the control group. Those patients on whom information of this sort was not provided by the medical records might differ from those on whom it was provided. In order to investigate this question as a possible source of bias, a comparison was made between the smoking histories as elicited in the home interview and as recorded in the medical records of the 175 interviewed patients with idiopathic thromboembolism and their controls.8

The smoking habits of 60 percent of the 175 patients with idiopathic thromboembolic disease were recorded in the medical abstract, as were 55 percent of the control group. Both groups were interviewed in their homes, and an independent statement was obtained as to their smoking status. As Table 6 shows, the smoking histories of the patients and controls obtained from medical records were similar to those obtained from the home interview. No impressive difference was found in smoking histories of women having such data in medical records compared to those not having this information recorded. This analysis suggests that incomplete data as recorded in the medical records may not necessarily contribute bias in a comparison of groups of patients.

Some comparisons were made with data from the National Health Survey for women of the same age groups. The latter were obtained from a probability sample of the entire population of the United States. Admitting the geographic disparity, the comparison was still considered justified, with caution in the interpretation of similarities and differences. For such physical attributes as blood pressure, even considering differences in techniques of measurement, the National Health Survey examination data are probably reasonably safe to use as a representation of the population values. It should be mentioned, also, that blood pressure is lowered with bed rest and that blood pressures were taken on ambulatory subjects in the National Health Survey. For some other attributes, such as the serum cholesterol level, the National Health Survey data may be less comparable.

The comparison groups used in this study are not adequate for all analyses, since the criteria for selection used in the original thromboembolism study8 introduce biases in the definition of patient groups; however, the criteria for selection were medical or surgical conditions predisposing to thromboembolism and did not include personal factors (age, race, religion, marital status, or smoking habits) or the use of oral contraceptives. Regarding preexisting medical conditions (eg, hypertension or diabetes), the best comparisons are with the National Health Survey data as representative of the general population.

The most impressive of the associations found in this study is with diabetes mellitus, but a definite association was also found with a history of increased cigarette smoking, presence of hypertension, and probably hypercholesterolemia. Each of these factors has been studied in a community sample of men and women over 45 years of age and was found to contribute significantly to the risk of myocardial infarction.24 No population data are available for younger female subjects, but this study suggests that these same factors operate in younger female subjects also. In addition, this study provides some evidence of an association between oral contraceptive usage and myocardial infarction (one-third of the

Table 6—Comparison of Smoking Habits Given in Hospital Records with Those Elicited on Subsequent Interviews

<table>
<thead>
<tr>
<th></th>
<th>Idiopathic Thromboembolism</th>
<th>Matched Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>State-</td>
<td>No State-</td>
</tr>
<tr>
<td></td>
<td>ment in</td>
<td>No</td>
</tr>
<tr>
<td>No. of patients</td>
<td>104</td>
<td>71</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>46 (44)</td>
<td>...</td>
</tr>
<tr>
<td>Occasional smoker</td>
<td>9 (9)</td>
<td>...</td>
</tr>
<tr>
<td>Light smoker</td>
<td>11 (11)</td>
<td>...</td>
</tr>
<tr>
<td>Moderate smoker</td>
<td>27 (26)</td>
<td>...</td>
</tr>
<tr>
<td>Heavy smoker</td>
<td>11 (11)</td>
<td>...</td>
</tr>
<tr>
<td>Subsequent interview</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>45 (43)</td>
<td>29 (41)</td>
</tr>
<tr>
<td>Occasional smoker</td>
<td>11 (11)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Light smoker</td>
<td>7 (7)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Moderate smoker</td>
<td>30 (29)</td>
<td>25 (35)</td>
</tr>
<tr>
<td>Heavy smoker</td>
<td>11 (11)</td>
<td>3 (4)</td>
</tr>
</tbody>
</table>

*Table values are numbers of patients; numbers within parentheses are percentages. Current use of cigarettes was classified as follows: occasional, does not smoke daily; light, less than 10 cigarettes daily; moderate, 10 to 20 cigarettes daily; and heavy, 21 or more cigarettes daily.
patients with myocardial infarction and 6 percent of the controls in the group aged 35 to 39 years had such a history recorded in the hospital records). The question cannot be settled with complete satisfaction from our data because of the lack of an optimal control group and the absence of interview data.

Regarding younger women with myocardial infarction, an increasing number of case reports and clinical series have appeared that suggest a possible association with oral contraceptives. Oliver has been interested in myocardial infarction in younger women and reported on 22 patients aged 31 to 41 years. Eleven (50 percent) had been using oral contraceptives, which was believed to be a higher proportion than the use in the general population of similar ages (estimated to be 4 percent in 1965 up to 13 percent in 1969, during which interval Oliver's patients were collected). The characteristics of the patients using and not using the oral contraceptives were similar, and both had an excess of carbohydrate intolerance, hypertension, hypercholesterolemia, and excess cigarette smoking. During the following three-year period, from 1970 through 1972, an additional 22 women (aged 31 to 45 years) with acute myocardial infarction were seen, and six (27 percent) had been taking oral contraceptives. Among the nine women aged 40 years or less, five had been taking oral contraceptives, while three of the other four had been sterilized by tubal ligation. All women had risk factors, with no difference between those using and not using the oral contraceptives. It was suggested that oral contraceptives enhance the chance of developing myocardial infarction in women already predisposed for other reasons.

Our findings are similar to those of Oliver and of Radford and Oliver with respect to identifying predisposing risks among younger women with myocardial infarction. Also, we found no difference in the proportion using oral contraceptives among cases with and without the various risk factors (including obesity). Waxler et al. reported three cases of young menstruating women who had an acute myocardial infarction while taking oral contraceptives; all had normal serum lipid levels, but selective coronary arteriographic studies showed a single, smooth, occluding lesion of the left coronary artery in each case, in contrast to the diffuse changes usually seen with atherosclerosis. Weiss described two young women without predisposing factors who had acute myocardial infarction while using oral contraceptives. Postmortem examination in the fatal case revealed minimal arteriosclerotic changes in the coronary arteries. Most recently, Friedlander and Snell reported on nine women under the age of 40 years with an acute coronary occlusive episode during a three-year period (December 1971 through November 1973). All seven of the patients who were not either pregnant or exposed to ergotamine-containing drugs had been taking oral contraceptives.

Results of earlier epidemiologic studies showed limited or no association between myocardial infarction and the use of oral contraceptives, but more recent investigations have revealed an increased relative risk of nonfatal and fatal infarction in oral contraceptive users. In England, Inman and Vessey investigated 54 deaths from coronary thrombosis, which occurred in patients who had used oral contraceptives, whereas 11.4 would be expected from the experience of the control women. This difference is not statistically significant, but if the 15 obese patients, none of whom had used oral contraceptives, are excluded, the difference attains statistical significance among the 20- to 34-year-old women of low parity (P < 0.01). Vessey and Doll, in their second report on oral contraceptives and thromboembolism, identified and interviewed 17 patients surviving coronary thrombosis who were married women aged 16 to 40 years. Two (12 percent) of the patients had been using oral contraceptives at the onset of their illness, and 2.1 were expected from the experience of controls of similar age and parity. These investigators noted more cigarette smoking and some excess weight among the coronary patients. Thus, no association of myocardial infarction and oral contraceptive use was found in that small sample.

In Denmark, Fischer and Mosbech investigated fatal cases of myocardial infarction during 1967 to 1968 in women 30 to 44 years of age and found that 15 percent used oral contraceptives. Although this overall proportion corresponded to usage in the general population, a further subdivision of the data showed that 25 percent of the patients aged 30 to 39 years were users, suggesting an association in women under the age of 40 years. In Goteburg, Sweden (with a population of about 445,000 persons in 1968), Bengtsson et al. studied women under the age of 57 years who had been admitted to the hospital during the period of 1968 to 1970 with an acute myocardial infarction. Among the 47 cases, 11 patients were premenopausal, and none had ever used oral contraceptives, but only one (37 years old) was under the age of 43 years. The number of premenopausal patients with myocardial infarction included in this study is also insufficient to evaluate an association with oral contraceptive usage.

On the basis of reports received by drug safety committees in the United Kingdom, Sweden, and
Denmark, Inman et al. analyzed thromboembolism following the use of oral contraceptives and found a relatively higher number of patients with coronary thrombosis who were using oral contraceptives with high doses of estrogen than might be expected. These data suggested an effect of the estrogen component of the oral contraceptives. In the Coronary Drug Project, a regimen of conjugated estrogens (5 mg daily) had to be discontinued because the patients in this group experienced an excess risk of myocardial infarction and other thromboembolism compared with the placebo group.

The Royal College of General Practitioners' ongoing prospective oral contraception study has last reported five cases of acute myocardial infarction in some 35,000 women-years of cumulative observation of oral contraceptive users (13/100,000 standardized rate) vs one case in some 60,000 women-years of cumulative observation in prior and never users (less than 2/100,000 standardized rate). The investigators concluded that numbers are as yet too small to justify any valid conclusions, although the difference is statistically significant (P < 0.05).

Mann et al. studied 63 married women under the age of 45 years who had been hospitalized for myocardial infarction during the period of 1968 to 1972 and compared them to 189 hospitalized controls discharged with acute medical or surgical conditions or after elective surgery who were matched to the cases by marital status, age, and year of admission. During the month before admission, 29 percent of the patients with myocardial infarction and 8 percent of the controls had used oral contraceptives (P < 0.001). A similar proportion had only used these agents more than one month before admission (10 percent and 12 percent, respectively). Cigarette smoking (and especially 20 cigarettes or more per day) was reported significantly more often by the patients with myocardial infarction than by controls, and a significantly greater proportion of patients with myocardial infarction had been treated for hypertension, diabetes, preeclampsia, and obesity. The mean levels of both serum cholesterol and serum triglycerides were substantially higher in the patients with myocardial infarction. The relative number of patients with myocardial infarction increased in comparison to controls with increasing numbers of risk factors (including use of oral contraceptives), indicating synergism among the factors studied. Based on certain assumptions of representativeness of admitted patients and oral contraceptive usage, estimates were made of the annual hospital admission rates of nonfatal myocardial infarction in married women aged 30 to 39 years. The rate was 2.1/100,000 among women not using oral contraceptives vs 5.6/100,000 among users. The comparable rate for women 40 to 44 years of age was estimated at 9.9/100,000 and 56.9/100,000, respectively.

Mann and Inman performed a comparable type of case-control study, investigating 219 deaths during 1973 from myocardial infarction in women under the age of 50 years, and compared their histories to those of living controls selected from the same general practices and matched on age and marital status. In the total groups, 21 percent of the cases of myocardial infarction had a history of oral contraceptive usage in the month before death, compared to 10 percent among controls (P < 0.001). Among subjects under the age of 40 years, 45 percent of the cases of myocardial infarction and 22 percent of controls had such a history (P < 0.001). Excluding subjects who had received any form of treatment for either hypertension or diabetes, 26 percent of the cases of myocardial infarction and 11 percent of the controls were "current" users (P < 0.01). However, it was not possible to study any interaction of cigarette smoking on the association of oral contraceptive usage and myocardial infarction, since data on smoking could not be obtained precisely. The patients with myocardial infarction had used the preparations for a longer average interval than the controls, 70 percent having a total duration of use of more than two years vs 42 percent of controls. In necropsy reports, coronary arterial thrombus was mentioned more frequently in users at the time of death (83 percent) than in nonusers (55 percent). Annual risks of death from myocardial infarction were estimated to be 1.9/100,000 women aged 30 to 39 years not using the oral contraceptives vs 5.4/100,000 in users. In the group aged 40 to 44 years, the annual estimated death rates were 11.7/100,000 and 54.7/100,000, respectively.

Whether the association of oral contraceptive usage and myocardial infarction found in these recent British case-control studies is causal or reflects an association of such drug use with some other factors is difficult to determine. Following these studies, the Food and Drug Administration sent a warning bulletin to medical professionals, suggesting that patients over 40 years using the oral contraceptives switch to another method of fertility control.

The data on women from our study and from other studies suggest an association of myocardial infarction and oral contraceptive usage which requires further investigation. Although the relative risk of developing myocardial infarction among oral
contraceptive users is not precisely known, it is estimated to be at least twofold in the group aged 30 to 39 years and about fivefold in the group aged 40 to 44 years.\(^4\) The majority of women reported to have myocardial infarction while using the oral contraceptives had at least one other risk factor predisposing to disease. The mechanism by which oral contraceptive usage may either contribute to or precipitate myocardial infarction is unknown. These agents have been shown to raise the levels of serum triglycerides, cholesterol, and lipoproteins of low density and very low density,\(^5\) such changes possibly predisposing to the development of atherosclerosis;\(^6\) however, coronary arteriographic changes have been found\(^8,9\) which are segmental and smooth and tend to be proximal and to spare the remaining coronary arterial tree, unlike the diffuse changes in atherosclerosis. Histologically, arterial lesions found in women dying while on a regimen of oral contraceptives have shown a characteristic intimal hyperplasia with luminal occlusion and without evidence of atherosclerosis, thrombosis, or fibrinoid necrosis;\(^10,11\) however, abnormalities of clotting factors and platelet function cannot be excluded as contributing to these vascular changes.\(^12\) In addition, hypertension has been reported to develop in certain patients while they are taking oral contraceptive pills\(^13\) and to normalize when the medication is discontinued.\(^14\) In population studies, the use of oral contraceptives is associated with a slight but definite increase in mean blood pressure.\(^15,16\) which might be an additional mechanism whereby such medications predispose to myocardial infarction in susceptible persons.

Further investigation of the relationship of oral contraceptive usage, both past and current, to the risk of developing myocardial infarction is needed in women of differing ages and with varying risk factors for this disease. Such studies promise a better understanding of the physiologic and pharmacologic effects of these sex steroids and may also reveal clues to the natural occurrence of myocardial infarction. For the present the consensus of available data indicates an additive effect of oral contraceptive usage to the recognized risk factors (including age) and warrants careful consideration in the use of these agents in higher risk or older patients.

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