CORONARY DISEASE SEVERITY AT NECROPSY*

BY

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One of the most objective clinical manifestations of coronary disease is cardiac infarction. Two main pathological processes may be implicated in its pathogenesis: first, the degree of disease in the vessel wall, and secondly, the presence of disease within the arterial lumen in the form of an occluding thrombus. Because of this potentially dual pathogenesis, there is a distinct possibility that any of the lipid abnormalities associated with the development of cardiac infarction, e.g. a high serum cholesterol level, could be relevant either to the degree of disease in the vessel wall, or alternatively to thrombosis itself, for occluding or near-occluding thrombi are found in over 90 per cent of recent infarcts (Mitchell and Schwartz, 1963). We have, therefore, made an attempt to assess the relationships between the amount of the various macroscopic types of coronary artery disease and age, diastolic blood pressure, heart weight, post-mortem serum cholesterol, and total coronary artery area. These findings are presented and discussed.

SUBJECTS AND METHODS

During the years 1962–63 we studied the coronary arteries of 206 patients (122 male, 84 female) dying in the Royal Adelaide Hospital, South Australia. This unselected necropsy sample initially comprised all cases including traumatic deaths presenting for necropsy examination on Wednesdays and alternate Sundays, but throughout the latter part of the study consecutive patients were admitted to the series: for each of these patients, the age, sex, and blood pressure levels were abstracted from the hospital in-patient notes when available. Wherever there was doubt as to the validity of the pressure records thus obtained, as in cases with haemorrhage, cardiac infarction, or strokes, an attempt was made to determine representative values from either the hospital out-patient notes, or from the patients’ private medical attendants. In 15 of the 206 patients, valid pressure records were not available from the above sources.

Post-mortem Serum Cholesterol. Total serum cholesterol was determined using modifications of the methods of Zlatkis, Zak, and Boyle (1953), and Zak (1957). A standard volume of serum (0.2 ml.) was heat-extracted with an alcohol-acetone mixture and aliquots of this extract were evaporated to dryness. This residue was dissolved in glacial acetic acid, and the colour developed by the addition of a mixture of ferric chloride in sulphuric acid.

Blood was removed from the heart while in situ with a 20 ml. syringe inserted in the right atrium, care being taken to avoid any dilution of the blood with serous fluid from the pleural or pericardial cavities. In 5 of the 206 patients the blood became gelatinous and would not separate on centrifugation.

Fifteen of the 206 patients had a previous serum cholesterol estimation, at intervals ranging from several hours to two years before death. In Fig. 1, these ante- and post-mortem cholesterol levels are compared. The post-mortem levels are on the average 33 mg./100 ml. higher than the ante-mortem levels, and the cor-

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731
regression of interest is significant, then inclusive in metric method centimetres was visual then halved. When the individual knowledge raised plaque, by part or hemorrhage, with covered proof of peri-adventitial debris can cork on segments changes Two of lesions areas of arteries was traced with a pencil. Four macroscopic types of plaque were recognized as suggested by the World Health Organization (1958): (1) Flat sudanophilic—fatty streaks; (2) raised sudanophilic; (3) raised non-sudanophilic—fibrous plaques; (4) complicated plaques—plaques showing ulceration, thrombosis, hemorrhage, or calcification. Different symbols were used on the tracings to differentiate the four types of plaque, as shown in Fig. 2, where it can also be seen that the variably short left coronary trunk was considered as part of the main left anterior descending artery. All traces, and subsequent planimetry, were performed without knowledge of the clinical details of the cases under investigation.

Planimetric Assessment. The trace was examined, and all the lesions of each macroscopic type were numbered in sequence for each of the 3 arterial branches. The area of the branches, and the area of each of the individual lesions was then measured with a rolling-wheel planimeter (Allbrit) calibrated to read in square centimetres (cm²). In all instances the tracing point was taken twice around each area, and the readings were then halved. For each of the 3 coronary artery branches we recorded the total arterial area and the areas affected by the four types of lesions. The reproducibility and observer error of this tracing and planimetric method have been evaluated by Cranston et al. (1964) who found it to be far more satisfactory than simple visual assessment.

Statistical Analysis. Both simple and multiple regression analyses were employed. The former, of interest in their own right, are also an important aid in the selection of determining variates for the multiple regression analyses.

The multiple regressions computed were designed to account for variability in each of the variates 6–11 inclusive in terms of the variability of the first 5 variates. If in a multiple regression, two or more factors are significant, then they exert influences that are to some extent at least independent of each other. In studies

**FIG. 1.—Correlation between ante-mortem and post-mortem total serum cholesterol levels.** ($r=0.8661$; $p<0.001$.)
CORONARY DISEASE SEVERITY AT NECROPSY

EXPERIMENT 43.

Fig. 2.—Example of a coronary artery trace, showing the arteries studied. R.C., right coronary artery; L.A.D., left anterior descending artery; L.Circ., left circumflex artery.

such as this where some of the determining variates are related, it is important to determine which variates exert independent effects.

RESULTS

Of the 206 unselected necropsy cases collected for study, 24 were excluded from statistical analysis for the following reasons: in 15, valid blood pressure records were not available; in a further 5 we were unable to determine serum cholesterol levels; and in 4, one or other of the 3 coronary artery branches was anatomically absent. The sample means and variance of the remaining 182 patients comprising this necropsy sample, together with a numerical key to the 11 variates analysed are detailed to Table I, and their age and sex distribution are given in Table II.

Diastolic Blood Pressure and Coronary Disease Severity. The significance of diastolic blood pressure (variate 2) has been determined using linear and multiple regression analyses. It is obvious from Tables III–VI that the coronary area affected by fatty streaking is unrelated to the diastolic blood pressure level in either males or females considered separately, or in males and females combined. This finding contrasts with the results obtained for the other macroscopic types of lesions, namely raised sudanophilic plaques (variate 7), fibrous plaques (variate 8), total disease (variate 10), and total disease excluding fatty streaking (variate 11). Complicated plaques, however, show no such relation with the diastolic pressure on either linear or multiple regression analyses, and in this respect behave similarly to simple fatty streaking.
### TABLE I
KEY TO VARIATES STUDIED, AND SAMPLE MEANS AND VARIANCES

<table>
<thead>
<tr>
<th>Key to variates analysed</th>
<th>Males (N=110)</th>
<th>Females (N=72)</th>
<th>Males and females (N=182)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Variance</td>
<td>Mean</td>
</tr>
<tr>
<td>1 Age (yr.)</td>
<td>64.9</td>
<td>222.9</td>
<td>62.4</td>
</tr>
<tr>
<td>2 Diastolic blood pressure (mm Hg)</td>
<td>95.0</td>
<td>572.5</td>
<td>99.4</td>
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<tr>
<td>3 Heart weight (g)</td>
<td>447.1</td>
<td>14770</td>
<td>376.9</td>
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<tr>
<td>4 Post-mortem total serum cholesterol (mg./100 ml.)</td>
<td>231.2</td>
<td>6765</td>
<td>272.0</td>
</tr>
<tr>
<td>5 Total coronary area (cm²)</td>
<td>24.7</td>
<td>34.46</td>
<td>21.8</td>
</tr>
<tr>
<td>6 Area of fatty streaking (cm²)</td>
<td>1.92</td>
<td>3.388</td>
<td>2.78</td>
</tr>
<tr>
<td>7 Area of raised sudanophilic plaques (cm²)</td>
<td>4.35</td>
<td>14.28</td>
<td>4.36</td>
</tr>
<tr>
<td>8 Area of fibrous plaques (cm²)</td>
<td>2.64</td>
<td>4.167</td>
<td>1.82</td>
</tr>
<tr>
<td>9 Area of complicated plaques (cm²)</td>
<td>1.34</td>
<td>8.820</td>
<td>1.34</td>
</tr>
<tr>
<td>10 Total disease (6+7+8+9) (cm²)</td>
<td>10.37</td>
<td>44.29</td>
<td>10.30</td>
</tr>
<tr>
<td>11 Total disease less fatty streaking (10–6) (cm²)</td>
<td>8.45</td>
<td>36.83</td>
<td>7.52</td>
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### TABLE II
AGE AND SEX DISTRIBUTION OF DATA

<table>
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<td>Age (yr.)</td>
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<td></td>
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<td>Number of patients</td>
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<tr>
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<tr>
<td>2 3 4 5 6 7 8 9 10 11</td>
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* Key is given in Table I.

### TABLE III
RESULTS OF LINEAR CORRELATION ANALYSES FOR MEN

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<tr>
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<td>0.0391</td>
</tr>
<tr>
<td>9</td>
<td>0.2644†</td>
</tr>
<tr>
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<td>0.2371</td>
</tr>
<tr>
<td>11</td>
<td>0.2291</td>
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Since 55 correlation coefficients are considered simultaneously, conservative tests of significance are employed. r values exceeding 0.2453 are significant at the 0.01 level (†), and values exceeding 0.3093 are significant at the 0.001 level (‡). Key to variates is given in Table I.
CORONARY DISEASE SEVERITY AT NECROPSY

TABLE IV
RESULTS OF LINEAR CORRELATION ANALYSES FOR WOMEN

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<thead>
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<th>Variate</th>
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<td>0.0091$</td>
<td>0.5072$</td>
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\[ r (0.01) = 0.3019; \ r (0.001) = 0.3803. \] Key to variates is given in Table I.

TABLE V
RESULTS OF LINEAR CORRELATION ANALYSES FOR MEN AND WOMEN COMBINED

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<td>0.2520$</td>
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\[ r (0.01) = 0.1902; \ r (0.001) = 0.2422. \] Key to variates is given in Table I.

It is of interest to note that in men variates 7, 8, 10, and 11, namely raised fatty and fibrous plaques, total disease, and total disease less fatty streaking were all significantly related to the diastolic blood pressure level at the 1 per cent level (Table VI). In women, however, only variate 11 (total disease less fatty streaking) showed a statistically significant relation \( (p < 0.05) \), though in the regression analysis of variates 7 and 10 diastolic blood pressure contributed materially without quite attaining significance. From these results it appears that the diastolic blood pressure level is a more important determining variate with respect to coronary disease severity in men than in women.

Serum Cholesterol and Coronary Disease Severity. Simple linear correlation analyses (Tables III–V) have revealed a statistically significant relation \( (p < 0.01) \) in men but not in women between the total serum cholesterol level, and the coronary artery area affected by raised sudanophilic plaques (variate 7), fibrous plaques (variate 8), and total disease less fatty streaking (variate 11). When men and women are combined, these relationships are obscured (Table V).

In neither men nor women, singly or in combination, is there any significant correlation between the total serum cholesterol level and the amount of fatty streaking or complicated plaques (Tables III–V). This finding, when considered in conjunction with the blood pressure findings, emphasizes the differential behaviour of these two variates, and the other types of lesions.

The statistical significance of total serum cholesterol as a determining variate for coronary disease severity was further explored by multiple regression analyses (Table VI). In men we found a significant correlation \( (p < 0.05) \) between the total serum cholesterol level and the extent of raised fatty and fibrous plaques, and total disease less fatty streaking (variates 7, 8, and 11). Total serum cholesterol (variate 4) contributed considerably to the regression for variate 10, or total disease, but
SCHWARTZ, STENHOUSE, TAYLOR, AND WHITE

TABLE VI
RESULTS OF MULTIPLE REGRESSION ANALYSIS EXCEPT WHERE INDICATED

<table>
<thead>
<tr>
<th>Sex</th>
<th>Determining Variates</th>
<th>Residual mean squares</th>
<th>Multiple correlation coefficient (R)</th>
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<td>Student's &quot;t&quot; values</td>
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<tr>
<td></td>
<td>Dependent variates</td>
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<td>Diastolic blood pressure (2)</td>
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<tr>
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</tr>
<tr>
<td>7</td>
<td>3.14†</td>
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<td>4.14‡</td>
</tr>
<tr>
<td>10</td>
<td>1.89 NS</td>
<td>---</td>
<td>3.31†</td>
</tr>
<tr>
<td>11</td>
<td>2.41*</td>
<td>4.03‡</td>
<td>4.61†</td>
</tr>
<tr>
<td>Males and</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>females</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=182</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>---</td>
<td>---</td>
<td>-2.51*</td>
</tr>
<tr>
<td>7</td>
<td>4.12‡</td>
<td>2.27*</td>
<td>7.40†</td>
</tr>
<tr>
<td>8</td>
<td>2.51*</td>
<td>2.08*</td>
<td>5.30†</td>
</tr>
<tr>
<td>9</td>
<td>3.04†</td>
<td>2.57*</td>
<td>---</td>
</tr>
<tr>
<td>10</td>
<td>1.85 NS</td>
<td>2.04*</td>
<td>9.78†</td>
</tr>
<tr>
<td>11</td>
<td>1.82 NS</td>
<td>3.20†</td>
<td>1.87 NS</td>
</tr>
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* Denotes p less than 0.05.
† Denotes p less than 0.01.
‡ Denotes p less than 0.001.
§ Linear correlation coefficient.

did not achieve statistical significance. In women the only significant correlation to emerge was for fibrous plaques (p<0.01). In neither men nor women did the area affected by complicated plaques (variate 9) show any significant correlation with the total serum cholesterol level.

A curious pattern emerged when fatty streaking was considered (Table VI). In men we found a statistically significant negative correlation (p<0.05) between the amount of fatty streaking and the total serum cholesterol level. Women, however, showed neither a significant negative nor a positive correlation. Combining men and women provided no such correlations, and the relation between serum cholesterol levels and the other variates became less conclusive.

Age and Coronary Disease Severity. Simple linear correlation analyses (Table III–V) have revealed that age and some of the other variates are significantly related. Thus in men there is a statistically significant relation between age and the amount of complicated plaques (variate 9), while in women no such relation can be seen, though age and variates 3, 5, 10, and 11 are significantly related. Combining men and women, it can be seen that as well as these relations the correlation between raised sudanophilic plaques and age also becomes statistically significant (p<0.01).

With multiple regression analyses (Table VI), the only significant relations to emerge between age and coronary disease severity are for complicated plaques in men, and men and women combined (p<0.01). In the latter, age contributed considerably to the regressions for total disease, and total disease less fatty streaking (variates 10 and 11), but did not quite attain statistical significance. These findings suggest that though some components of coronary disease severity are significantly related to age on the basis of simple linear correlation analyses, this relation is to some extent determined by other age-dependent variates, including heart weight, total coronary area, and diastolic blood pressure.
**CORONARY DISEASE SEVERITY AT NECROPSY**

*Heart Weight and Coronary Disease Severity.* From Table VI it can be seen that in women heart weight is a statistically significant determining variate with respect to all dependent variates with the exception of fatty streaking (variate 6) and fibrous plaques (variate 8). In men and women combined, heart weight is a significant determining variate for all six dependent variates, though it should be noted that the relationship with fatty streaking (variate 6) is negative.

*Coronary Area and Coronary Disease Severity.* In both men and women, and in men and women combined, we have found (Table VI) that all the variates of coronary disease severity with the notable exception of complicated plaques (variate 9) are significantly related to the size (area) of the coronary arteries ($p<0.001$). These findings suggest that the coronary area at risk is an important factor in determining the extent of disease.

**DISCUSSION**

The widely accepted relation between coronary artery disease severity and various serum lipid abnormalities including a high serum cholesterol level has been largely based on inference rather than on fact. Several points in this perplexing jigsaw are reasonably clear. First, from the pioneer studies of Kinsell and his associates (1952, 1958) and the extensive field studies of Keys *et al.* (1958), it is now accepted that both the quality and quantity of dietary fats play an important role in determining the serum cholesterol level in man. Secondly, there is little doubt that the plasma lipid levels are raised in patients with clinical coronary artery disease, an observation supported by many workers, which over the past few years has been convincingly established by Dawber and his associates (1962) from their excellent longitudinal study at Framingham. In reporting their findings after a period of 8 years, they concluded that a high initial serum cholesterol level, and also raised blood pressure level were significantly associated with an increased risk of developing clinical “coronary heart disease”.

Whether it is reasonable to extrapolate from their data to a correlation between the serum cholesterol level and the degree of coronary artery disease, or alternately to assume a relationship between the former and the presence of an occluding coronary artery thrombus, we are uncertain. The present study suggests that the first alternative is likely to be correct, though the possible validity of the second alternative is certainly not excluded. We have found that the total serum cholesterol level, determined on post-mortem blood, is a statistically significant determining variate for some of the components of coronary disease severity in both men and women (Table VI), and, moreover, that the effect is more important in the former than in the latter. It is also of interest to note that in neither men nor women did we find a significant positive correlation between the extent of fatty streaking and the serum cholesterol level, a finding that emphasizes the differential behaviour of fatty streaking and raised fatty and fibrous plaques. This potentially important difference has already been discussed by Schwartz and Mitchell (1962). The negative correlation for fatty streaking noted in Table VI could well mirror the positive correlation observed for the other types of lesions.

Thrombosis is but one of the four parameters considered under the term complicated plaque. In neither men nor women did the extent of this type of plaque (variate 9) show any correlation with the serum cholesterol level. In this study both calcification and ulceration were more extensive components of the complicated plaque than thrombosis itself. This dilution effect, together with the essentially heterogeneous composition of the complicated plaque, could easily obscure any relation, if there is one, between serum cholesterol levels and thrombosis. Because of this difficulty we recommend that thrombosis be considered separately in any future pathological or epidemiological studies.

The only other attempt to relate the degree of coronary artery disease at necropsy with the serum lipid levels was made by Paterson, Armstrong, and Armstrong (1963) who after a meticulous study failed to establish any correlation between these variables. Many factors, including differences in methods of assessing disease severity, the selection of cases, and even the number of cases studied could singly, or in combination, account for the different findings. Although we have clearly demonstrated a statistical correlation between the terminal serum cholesterol level and some of the
components of coronary disease severity at necropsy, it would be premature to conclude that these two variables are causally related.

Mitchell, Schwartz, and Zinger (1964) have already shown a clear relation between aortic disease severity (excluding fatty streaking and complicated plaques) and the diastolic blood pressure levels in a large unselected necropsy survey. In many respects the findings of this study confirm their observations, for neither the extent of fatty streaking nor the extent of complicated plaques in the coronary arteries has shown any correlation with the blood pressure level, while the remaining macroscopic types of lesions show a variable relation with the latter in both men and women (Table VI). As with the serum cholesterol level, the level of diastolic blood pressure appears to be a more important determining variate in men than in women. These findings are generally consistent with the results of the Framingham study, and certainly suggest that raised blood pressure might play a role in the development of coronary artery disease. This has already been suggested by others including Davis and Klainer (1940). Such a conclusion must of course be considered with caution, for it is remotely possible that either a high blood pressure, or a high serum cholesterol level, could be overt manifestations of a more fundamental and as yet unrecognized cause of coronary artery disease.

Age is clearly an important determining variate for the extent of complicated plaques in men, and also in men and women combined (Table VI). In this latter combined group, age almost attains statistical significance for variates 10 and 11, while fatty streaking shows no such relation. It is obvious that some of these relations differ when simple linear correlation analyses are employed (Tables III-V), and age is clearly a less important factor in the multiple regression analyses. This observation emphasizes the fact that though age is by itself a significant determining variate, a proportion of the age-effect is due to other age-dependent variates. It is noted that the greatest rise in total disease less fatty streaking (variates 11) occurs in men aged 40–49, while in women the rise occurs some 10 years later in the age-group 50–59 years. This age and sex difference points to the possible protective effect of hormonal factors in premenopausal women, a phenomenon that has been described and reviewed by Oliver (1960).

From this brief discussion it must be obvious that coronary disease severity is statistically related to many factors including blood pressure and serum cholesterol levels, as well as to age, heart weight, and total coronary artery area. While the possible role of thrombosis in its aetiology and pathogenesis has received but scant mention in this discussion, it is possible that this could provide an alternative link between abnormal lipid metabolism on the one hand and the development of stenosing arterial plaques on the other.

**SUMMARY**

Quantitative planimetric methods for the assessment of coronary artery disease severity have been employed in this unselected necropsy study. We found statistically significant correlations between the extent of some of the components of coronary disease and diastolic blood pressure, post-mortem serum cholesterol levels, heart weight, age, and total coronary artery area. The relation between these variates differed in men and women.

A differential pattern of behaviour between fatty streaking and other macroscopic types of raised plaques was noted. No significant positive correlation between the extent of fatty streaking and either the diastolic blood pressure level or the post-mortem serum cholesterol level was observed, and the latter was found to correlate closely with the level determined during life. These findings have been discussed with reference to their possible significance in the aetiology and pathogenesis of coronary artery disease.

We are indebted to Miss V. Vainickis for her invaluable technical assistance throughout the study; to Professor J. S. Robertson and the staff of the University Department of Pathology for their co-operation, to Mr. W. Nolan and J. A. Smith for the photographs, and to Miss D. Tidswell for computing assistance.
CORONARY DISEASE SEVERITY AT NECROPSY

REFERENCES


Coronary disease severity at necropsy.

C J Schwartz, N S Stenhouse, A E Taylor and T A White

Br Heart J 1965 27: 731-739
doi: 10.1136/hrt.27.5.731

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