

THE AETIOLOGY AND POSSIBLE PREVENTION OF MYOCARDIAL INFARCTION*

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SUMMARY

The subjects of this study were 250 cases of myocardial infarction treated personally. Despite lack of proof that the relationship is causal there is a clear association with obesity, excessive cigarette smoking, hypertension, emotional stress, hyperuricaemia and in qualified groups hyperlipidaemia. Until the aetiology of myocardial infarction has been clarified, it would appear reasonable to treat these factors so as to perhaps afford potential myocardial infarction sufferers some prophylaxis.

Indirect clinical evidence is presented, which, correlated with the structural chemical similarities between cholesterol, sex hormones, vitamin D₃ and cortisone, suggests that future research be guided along these lines in the hope that a common denominator will eventually be discovered.

Several epidemiological studies have indicated that people with certain characteristics form a high-risk group, in which the chances of sustaining myocardial infarction are higher than in the general population. Nevertheless, the importance of these various characteristics and, in fact, the entire causation of myocardial infarction remain controversial and confusing. The present study was undertaken in an attempt to assess various possible aetiological factors in the hope that their elimination may afford some protection to potential sufferers from myocardial infarction.

MATERIAL AND METHODS

The study included 250 consecutive cases of acute myocardial infarction treated personally, initially in private practice and then in the medical unit of Discoverer's Memorial Hospital, Florida. The criteria used for diagnosis were the clinical history and examination with ECG evidence of pathological Q waves, S-T segment changes, later T-wave inversion, a falling R wave in the precordial leads, complete left bundle-branch block and, where necessary, significant and transient elevation of serum LDH and SGOT levels.

RESULTS

Age and sex. The 250 patients comprised 171 males and 79 females. The age range for males was 27-84 years and for the females 42-85 years. At all ages males predominated, the ratio being over 5:1 in the under-50 age-groups. From the sixth decade the difference narrowed considerably to become negligible between the two sexes. Among males, 72 of 171 (42.1%) occurred under the age of 50, compared with only 13 of 71 females (18.3%). These differences are reflected in a positive- and negative-skewed frequency polygon (Fig. 1).

Inheritance. The old Arab proverb that 'you inherit your father's arteries' seemed to be correct to some extent for males, but in females the incidence did not seem to be related to that of either parent and no significant data could be obtained from the family history (Table I).

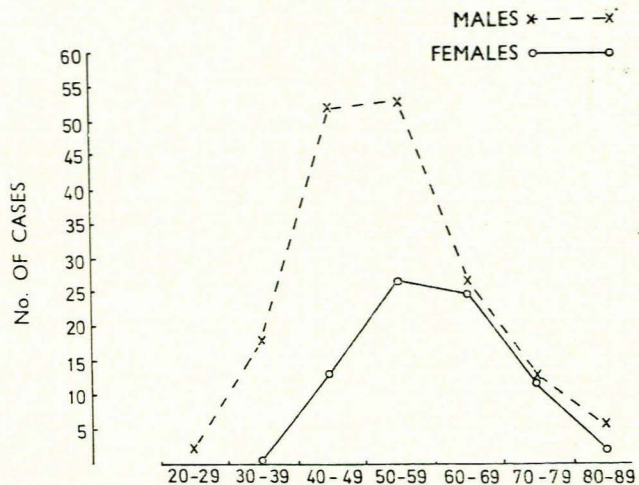


Fig. 1. Age incidence in 250 cases of myocardial infarction.

TABLE I. MYOCARDIAL INFARCTION IN THE FAMILY

	Females	Males
Father	1	12
Mother	7	6
Both parents	1	7
Siblings	4	11
Parents + siblings	5	11
Total	18 (23%)	47 (28%)

Obesity. Using standard height, weight and age tables, individuals 9 kg above the mean were defined as obese. Different degrees of obesity were grouped together in this study. Results showed that there were more fat people with infarction than in the control group and that this applied more particularly to men (Table II).

TABLE II. OBESITY AND MYOCARDIAL INFARCTION

Age (yr)	Cases with infarction		Control series	
	Females	Males	Females	Males
20-29	—	1	—	1
30-39	—	8	—	1
40-49	5	17	10	8
50-59	14	20	14	9
60-69	15	13	4	8
70-79	8	14	4	5
80-89	—	—	—	—
Total	42 (53.2%)	73 (42.7%)	32 (40.5%)	32 (18.7%)

Diabetes mellitus. Eleven patients had diabetes and the condition was more common in females (8 of 79 cases, 10.1%). In the under-50-year group there were 2 female diabetics among 13 cases of infarction (15.4%) and, while the figures are too small for statistical significance, the incidence does suggest that diabetes assumes a more important role in that group (Table III).

Uric acid. In 32 cases plasma uric acid ranged from

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TABLE III. DIABETES MELLITUS AND MYOCARDIAL INFARCTION

	Infarction	Diabetes	%
Total cases all ages			
Females	79	8	10.1
Males	171	3	1.8
Total < 50 years			
Females	13	2	15.4
Males	72	0	0

4.1 to 8.0 mg/100 ml (average 6.1) for males and from 3.0 to 11.9 mg/100 ml (average 6.3) for females. Although all the 16 males had levels under 8.7 mg/100 ml, 13 (81%) were above the 5.3 mg/100 ml normal mean. In the 16 females studied 7 had levels of over 6.3 mg/100 ml and 12 (75%) were above the 4.3 mg/100 ml normal mean (Fig. 2).

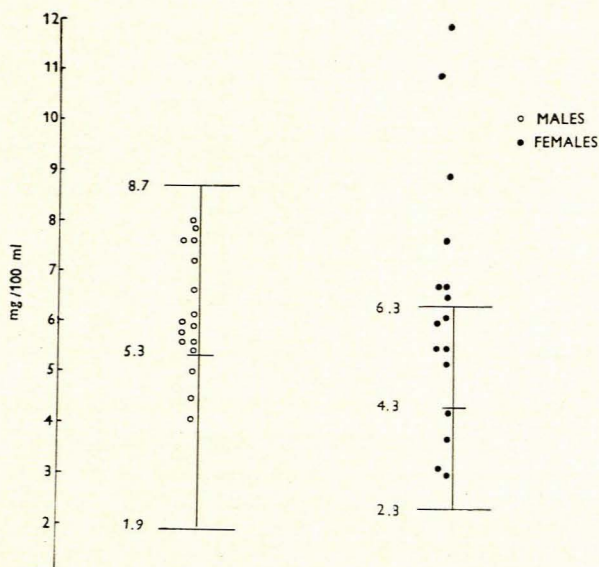


Fig. 2. Plasma uric acid.

Serum magnesium. Serum magnesium levels were studied in 30 consecutive cases and all fell well within the normal range with the scatter centred mainly on the mean level of 1.99 (Fig. 3).

Tobacco. There were slightly more abstainers and mild to moderate cigarette smokers in the control group. Among the pipe smokers, the number who had previously smoked cigarettes was unfortunately not collated. Cigarette consumption of more than 30 per day was considered heavy and only in this group was there a higher incidence among the myocardial infarction group (Table IV).

TABLE IV. TOBACCO SMOKING AND MYOCARDIAL INFARCTION

	Non-smoker	Mild <15 per day	Moderate 15-29	Heavy 30 and over	Pipe
Cases with infarction					
Males	50	23	33	50	15
Females	56	10	6	7	—
Control series					
Males	60	18	53	32	8
Females	60	8	7	4	—

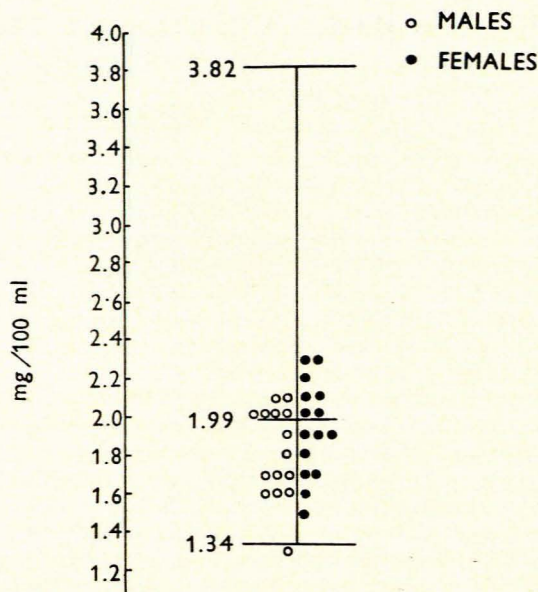


Fig. 3. Serum magnesium.

Peptic ulcer. Peptic ulcer was present in only 1 female. Of the males 9 had proved peptic ulcers and while the numbers are insufficient for statistical evaluation, the age correlation suggested an increasing trend in the younger age-groups (Table V).

TABLE V. PEPTIC ULCER AND MYOCARDIAL INFARCTION IN MALES

Age (yr)	Cases of cardiac infarction	No. of cases with peptic ulcers	% with peptic ulcers
Under 40	20	4	20%
40-49	52	3	5.8%
50-59	53	2	3.8%
60 and over	46	0	0%

Stress. While it is difficult to define stress and to differentiate at times physical from emotional, when patients stated that they had been under undue stress this was accepted. In all, 94 patients (38%) volunteered that stress had immediately preceded their infarction. This stress was of a physical nature in 9 cases, emotional in 79 and occurred postoperatively in 6 cases. The physical factors included sport, lawn mowing, chasing a thief, paroxysmal tachycardia and sexual intercourse. The emotional factors were financial, excitement at seeing relatives, losing a wife, playing poker, etc.

Calcium. Serum calcium levels were normal in 20 of 32 cases, slightly elevated at 5.6 mg in 1 male who died, and scattered below the 4.7 mg level in 11 cases (34.4%). Of the 32 patients studied, 24 (75%) had levels below the mean norm of 5 mg/100 ml (Fig. 4).

Hypertension. Diastolic hypertension, or a definite history thereof, was noted in 63 of 171 males and 45 of 79 females with a peak incidence in the 50-59 decade (Fig. 5). Conversion of these figures into a percentage showed that at all relevant ages the percentage of females with hypertension was, in fact, considerably higher than in males (Fig. 6).

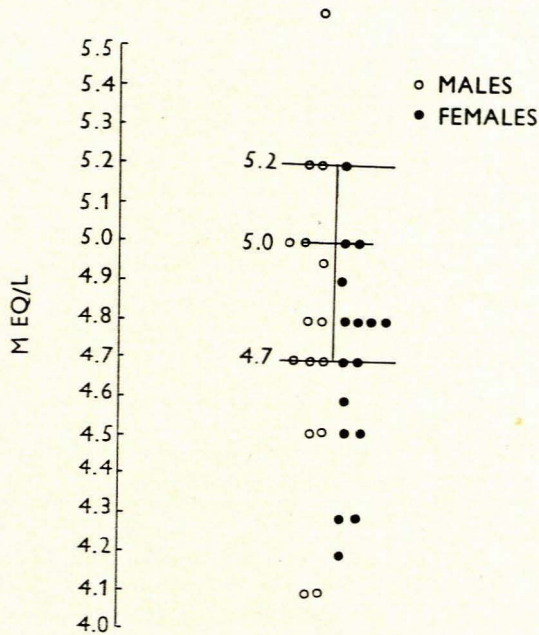


Fig. 4. Serum calcium.

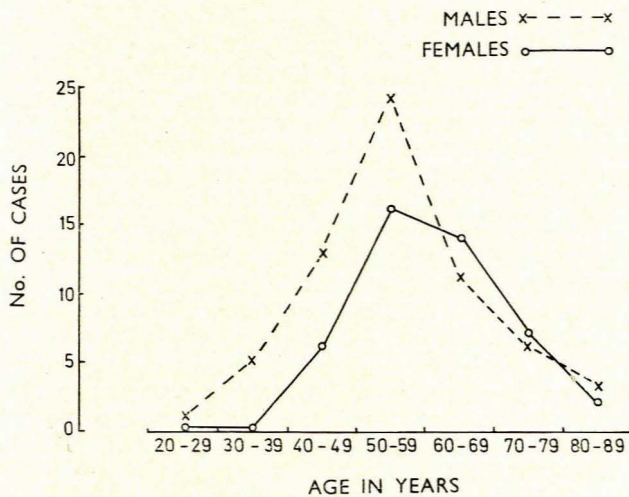


Fig. 5. Incidence of diastolic hypertension.

Vanillylmandelic acid (VMA) urinary levels were measured in 20 patients. Levels for males ranged from 4.5 to 24.4 (mean 13.3) mg/24 h and for females 2.5-25.3 (mean 10.6) (Fig. 7). In the 2 females and 2 males with levels of 18.0 and over, no history of drugs or dietary factors could be elucidated, nor was there a correlation with hypertension, cardiogenic shock or congestive failure. In 1 male (level 24.4) severe, acute emotional stress had accompanied the episode of infarction.

Blood lipids. Lipograms were performed on 70 males: 42 were normal and 28 abnormal. In 30 females 14 were normal and 16 abnormal. An arbitrary breakdown point at 50 years revealed that in men under 50, 53.8% had hyper-

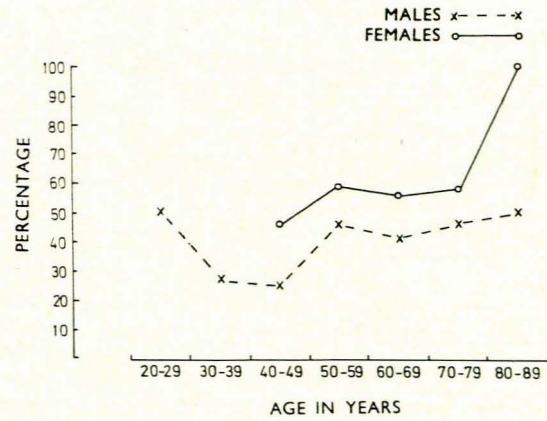


Fig. 6. Percentage of hypertensives in 250 patients with myocardial infarction.

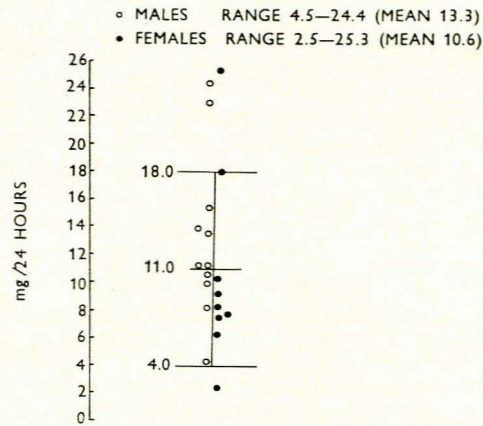


Fig. 7. Urinary vanillylmandelic acid.

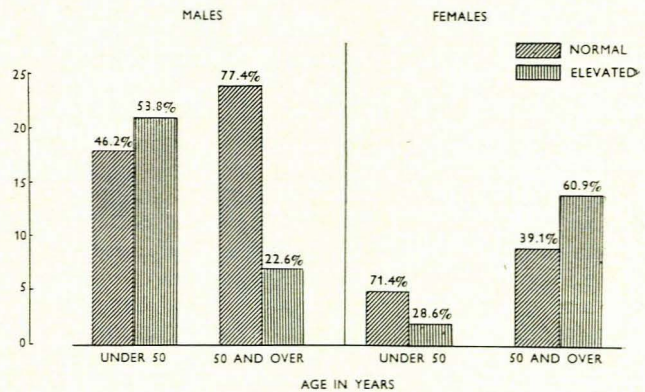


Fig. 8. Blood lipids in 100 cases of myocardial infarction.

lipidaemia while in the over-50-years group only 22.6% were abnormal. Females showed a negatively skewed distribution with 28.6% abnormal in the under-50 age-group and 60.9% abnormal in the over-50 age-group. Thus males tended to develop their hyperlipidaemia under the age of 50 and females over 50 years of age (Fig. 8). In 4 of 28 males and 8 of 16 females with distinctly abnormal

lipograms, the cholesterol levels were well within the normal range, indicating that serum cholesterol tests on their own can be very misleading.

DISCUSSION

The results of this series are disturbing, in that 20 men (11.7%) sustained their myocardial infarction under the age of 40, and 72 (42.1%) before they had reached 50 years. Statistics supplied by a leading South African life insurance society reveal that deaths due to myocardial infarction expressed as a percentage of number of deaths among policy holders during the period 1967-1969 reached 42% during one year. The increasing morbidity and mortality from coronary heart disease, particularly in men during the prime of life, is causing similar concern in the UK,¹ USA² and Australia.³

Magnesium blood levels not unexpectedly failed to show any data that may be relevant to the aetiology of infarction but were assessed because of the unscientific time-honoured view that parenteral injections of magnesium salts helped reduce the incidence of anginal attacks and because hypomagnesaemia is known to occur in hyperparathyroidism. In turn, it is known that idiopathic hypercalcaemia in children may cause, not only hypertension, but hypercholesterolaemia, both of which are well-known characteristics in the so-called 'high-risk' coronary group, even if the mechanism of hypertension is different.

This study was done in Johannesburg, a city with an average of 4 350 hours of sunshine per year. By comparison California has 3 220 hours, Swiss Health Resorts 1 760 and London approximately 1 500 hours annually.

The high incidence of myocardial infarction in South African Whites is in striking contrast to the rarity of the disease in the South African Bantu and the reasons for the differences remain obscure. We admit that urbanization may be increasing the incidence, that the South African Bantu do suffer from severe atherosclerosis outside the coronary tree, and that their lower blood lipid levels are possibly related to dietary factors. The possibility that the skin may in some way afford protection was also considered. Vitamin D₃ (cholecalciferol) is formed photochemically by sunlight from 7-dehydrocholesterol. Other substances with D-activity including vitamins D₂ (calciferol), D_{4/5} and D₆ are artificially produced by irradiation of ergosterol, of 22-dihydroergosterol, of 7-dehydro-sitosterol and of 2-dehydrostigmasterol, respectively. As in idiopathic hypercalcaemia, high doses of vitamin D can also cause hypercalcaemia and arterial hypertension. This, at present, is accepted as being due to a renal mechanism. Dissimilarities in molecular structure may profoundly alter biological effects but there is, nevertheless, a basic similarity between the cholesterol carbon skeleton and that of vitamin D₃ (Fig. 9). Perhaps in some way biochemical research could be directed at this level in the hope that it will elucidate other factors or even a common denominator in the pathophysiology of hypercholesterolaemia, hypercalcaemia, hypertension and even coronary atherosclerosis.

In 11 of the 32 (34.4%) patients studied serum calcium levels were lower than the accepted normal range and

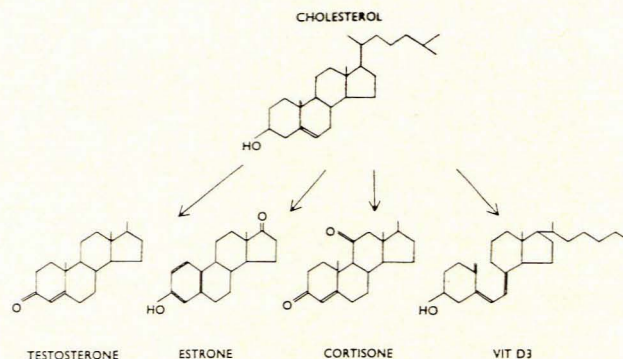


Fig. 9. Comparison of molecular structures.

24 (75%) below the mean norm of 5 mg/100 ml. These results appear to contradict any hypothesis in relation to hypercalcaemia. In view of the absence of evidence in favour of another theory, it was considered possible that in these patients, serum calcium levels were low because of tissue binding and that body, and particularly arterial reservoirs, were supersaturated, causing atherosclerosis.

Sex incidence results showed that myocardial infarction occurred 5 times more often in men under the age of 50 but from the sixth decade the sexual difference narrowed dramatically and for practical purposes disappeared. It may be argued that by the sixth decade susceptible males had died out, but these differences could also support the view that oestrogens protect females until the menopause and thereafter with oestrogen deficiency the incidence of infarction increases. However, to confuse the problem even further, there are reports that oral contraceptive pills containing oestrogens, particularly in higher dosages, increase the risks of thrombo-embolic disease,⁴⁻⁶ and that women prone to ischaemic heart disease may have an increased risk of developing myocardial infarction.⁷ Oliver and Boyd⁸ showed that oestrogen therapy in males did not increase the life-span of patients who had sustained myocardial infarction. This may be due to the fact that the dose of oestrogens was too small or that the damage had already been done. Cholesterol gives rise to androgens and androgens can be converted into oestrogens. There is a basic similarity in the molecular structure between these hormones (Fig. 9).

The sex incidence difference in this series may therefore be related to androgen rather than oestrogen. Perhaps androgens damage males earlier in life and when body supplies diminish, a relative hyperoestrogenaemia affords protection. In the case of females relatively higher androgen levels may develop with the menopause. The males in this series who had associated hyperlipidaemia were mainly in the under-50 age-group, with a positively skewed distribution, while females, conversely, had hyperlipidaemia over 50 years of age, with a negative skewed distribution. This may support further the hypothesis of such a hormonal imbalance.

The smoking habits of 4 120 men from Albany, New York and Framington in relation to coronary heart disease, showed that heavy cigarette smokers experienced a threefold increase in the incidence of myocardial infarction as compared with non-smokers and smokers of

pipes and cigars.⁹ In the present series, a consumption of more than 30 cigarettes daily was considered heavy, and only in this group was there a higher incidence of myocardial infarction than in control subjects (Table IV). The mechanism whereby heavy cigarette smoking may influence the incidence of myocardial infarction is obscure, but results from other parameters in this study suggest—and many cigarette smokers will agree—that people smoke more when under stress; it may not necessarily be the direct influence of tobacco but the underlying stress that is related to myocardial infarction.

Peptic ulcer is considered by many to be the result of a stress situation. The cases of proved peptic ulcer in this series were too few to warrant statistical evaluation, but did show an age trend favouring young males, the same group who had hyperlipidaemia. Stress and cortisone represent a biochemical *sine qua non* and the cholesterol carbon structure is convertible to cortisone (Fig. 9). A definition of stress may be open to criticism but 94 (38%) of the patients in this series volunteered acute and/or chronic stress preceding infarction. Some of these were quite dramatic.

Hypertension may be due to many causes, including emotional stress, and the frequency of this association confirms the findings of other workers. Based on a percentage factor, the present results indicate that at all relevant ages females were more often hypertensive (Fig. 6). The role of the sympathetic nervous system in the course of myocardial infarction was studied by Jewitt *et al.*¹⁰ who found raised urinary catecholamine levels in patients developing heart failure or cardiogenic shock. By contrast, in uncomplicated cases, a moderate rise in noradrenaline levels was associated with only transient rises in adrenaline levels. In another investigation, urinary catecholamine elevations occurred in some instances at times of psychological stress.¹¹

Vanillylmandelic acid (VMA) urinary levels were measured in 20 consecutive patients from this series in the hope that some objective evidence to support the stress hypothesis could be produced. In the four patients with levels of 18.0 mg/24 hours or more, there was no correlation with drugs, diet, hypertension, cardiogenic shock or congestive failure. In one male with a high VMA level severe, acute emotional stress accompanied the onset of infarction.

Many workers have observed the association of hyperuricaemia with atherosclerosis¹²⁻¹⁵ and, indeed, with coronary heart disease itself.¹⁶ In the present series, a majority of both sexes were above the mean, while in females a high percentage were frankly hyperuricaemic (Fig. 2).

The other metabolic disorder that has been postulated as predisposing to coronary heart disease is diabetes. In this series there were only 11 cases, with a breakdown suggesting that there may be an association in females

(Table III). Obesity was more common than in control subjects (Table II), while familial studies (Table I) suggested that men tended to inherit their father's arteries.

The characteristics which appear to be clearly associated with the development of myocardial infarction are obesity; excessive cigarette smoking; hypertension; physical and emotional stress; hyperuricaemia; peptic ulcer in males; diabetes in females; and in both sexes, depending upon age-groups, hyperlipidaemia (in males under 50 years of age and in females over 50 years). The association of these factors does not necessarily imply a causal relationship but, until the aetiology of this apparently multifactorial disease has been clarified, it would appear reasonable to look for these factors and treat them as a routine measure in the hope that the ultimate incidence of myocardial infarction will be reduced.

Realizing full well that even slight molecular changes profoundly alter action and effects, there is, nevertheless, a basic similarity between the structure of cholesterol, vitamin D₃, testosterone, oestrone and cortisone (Fig. 9). With the indirect clinical evidence presented to suggest a relationship between some of these biological and hormonal factors, further research at this level may help to solve the problem of myocardial infarction.

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