Selected Topics in Preventive Cardiology

Edited by Angelo Raineri
and Jan J. Kellermann

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Edited by

Angelo Raineri
University of Palermo Medical Center
Palermo, Italy

and

Jan J. Kellermann
The Chaim Sheba Medical Center
Tel-Hashomer, Israel

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PREFACE

The aim of the 2nd Course of the International School of Cardiology at "Ettore Majorana" was the discussion, scientific analysis, and critical appraisal of primary and secondary prevention in cardiology, especially concerning the coronary artery disease.

The predictive value of different risk factors, the problem of heredity, sociological and psychological perspectives, the impact of antiarrhythmic therapy, and the prevention of sudden death were only some of the many topics discussed.

Others, such as physical activity in primary and secondary prevention, the role of coronary bypass surgery in decreasing the mortality rate, the effects of drugs and comprehensive intervention programmes, as well as a critical appraisal of therapy in cardiac failure were given special attention.

In organizing this second Course, it was again a privilege and a challenge for the programme directors to conduct a scientific event which, as was demonstrated at the first course, represented an original and new approach to teaching. The illustrious international faculty, composed of well known scientists and experts in their fields, has contributed to the high academic level and quality of the lectures and the following discussions.

In our opinion, this successful undertaking would not have achieved its purpose and originality without the beautiful surrounding scenery and tranquility of Erice.

We should like to express our gratitude to the director of the Centre, Prof. Zichichi, and the Secretary of "Ettore Majorana," Dr. Gabriele, for their outstanding cooperation. The editors hope that a glimpse of the spirit of this second Course will be reflected in the volume.

Jan J. Kellermann
Angelo Raineri

Directors of the Course on
Prevention in Cardiology

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INTRODUCTION

The International School of Cardiology is engaged, as the other Schools in this Centre, in promoting scientific and cultural meetings.

In this direction we began our activity in 1979 with the Course on "Functional Evaluation and Rehabilitation in Cardiology."

Following this aim we are here to discuss the "Prevention in Cardiology."

On this occasion too Prof. Jan Kellermann, who I would like to thank deeply, gives us all his experience as a scientist and as a very keen organizer of cultural initiatives to offer this second Course every prerogative of success.

In the past culture was an estimated quality, a type of conscious ideal of human perfection; now it is considered as the social contest in which we are born and live.

Culture, in a sense would no longer be what we are trying to reach or to be, but the historic and sociological reality in which we are living and growing.

Stimulated by natural desire to search, discover and know which is typical of human beings, the modern cardiologist can use instruments of high technological significance so that the investigation, observation and interpretation of events can happen with the best penetrating capability.

Therefore it is necessary to stress that if as researchers we are prone to consider the advantages technology has given to scientific progress, on the other hand it is not possible to neglect that in general the transfer of technological development on the contest of social life has determined a situation in which the way of thinking has been modified, creating an upheaval in the habits of life. Thus nowadays, perhaps for this, we face a deep change in the spectrum of pathologies responsible for the causes of death, in which there is the prevalence of the chronic-degenerative component.

The profound changes of pathology during the last decade impose a radical change of purposes. The efforts, that up to now have been predominantly addressed toward a more important widening of our knowledge of the aspects of clinical diagnosis and therapy, have to be moved back towards the prevention.

In the Course we have got epidemiologists, cardiologists and cardiac surgeons together with the aim of giving a multidisciplinary order to a topic that is a strategic choice in confronting a problem of a great practical importance.

Firstly I would like to thank all the lecturers for showing a great sensitivity in accepting our invitation.

I would like to wish all the participants proficous work, in deepening their knowledge.

Angelo Raineri

Director of International
School of Cardiology
"Ettore Majorana Center"

HEREDITY, ATHEROSCLEROSIS AND CORONARY HEART DISEASE

Frederick H. Epstein

Institute of Social and Preventive Medicine
University of Zürich
CH 8006 Zürich

The familial-genetic aspects of coronary heart disease (CHD) are something of a stepchild in atherosclerosis research for, probably, two major reasons: (1) family studies are tedious and difficult, (2) professional geneticists who are needed as collaborators in this kind of work, sometimes tend to shy away from complex, polygenic situations, with the added problem of having to disentangle the influence of heredity from environmental factors. Yet, there is a trend toward including families in clinical-epidemiological investigations and genetic models to cope with the difficulties mentioned are beginning to be developed[1,2]. The statement has been made for many years that "the family history is important" with regard to susceptibility toward CHD but there is still no entirely satisfactory answer to the question how important it is quantitatively as compared with other risk factors and how importance relates to the age at which the disease presents[3-5].

In practice, it is asked to what extent coronary heart disease aggregates in families. This review will deal mostly with this question, rather than the equally important but relatively better studied matter of familial resemblance in CHD risk factors. However, even in this latter instance, much more is known about familial transmission in the top range of risk factor levels (e.g. the hyperlipidaemias) than in the mild and moderate range where most cases of CHD occur. The term "familial" rather than "genetic" has been used deliberately and consistently because families share their living habits as well as their genes and it is notoriously difficult to separate the two (the "nature-nurture" problem).

Important though it is to learn more about the risk carried by oneself if a close relative is affected with CHD, the statement not

infrequently heard that hereditary predisposition is the most important CHD risk factor is to be deplored. This is an unfortunate half-truth which detracts attention from the paramount influence of the environment on the causes and prevention of the disease. Of course, in a constant environment, biological variation is determined entirely by genetic predispositions. In so-called developed and more and more in developing countries, the majority of people in the population have adopted patterns of daily living which promote atherosclerosis and premature coronary heart disease. In such an all-pervading, detrimental environment, genetic factors must of necessity exert a decisive influence. On the other hand, there is every reason to believe that the big differences in the frequency of coronary heart disease between populations differing in living habits are largely determined by the environment, as are the marked secular changes which have occurred during the last decades, both upward and downward, in many countries.

Familial Clustering of Coronary Heart Disease

The earlier literature on this subject has been reviewed[2-6] and attention will be confined to more recent data. A Finnish Study is particularly instructive[7] (Table 1). The probands were all men who developed CHD before the age of 56. In one of the analyses shown, it is apparent that a brother of a patient with myocardial infarction prior to age 56 has a very high risk of dying of the disease himself by age 60, being around 7 times higher than the risk of a brother without such a "family history"; sisters also carry a higher risk, as do brothers of male probands with angina pectoris. In another analysis of the same series[8], the risk of a parent dying before age 70 is seen to be dependent on the age of occurrence of MI in the son, rising steeply with decreasing age (Table 2). Family studies amongst Japanese living in Hawai also suggest a decisive influence of the age at which CHD presents in the proband on the risk in his relatives[9]; the risk of developing CHD in siblings of an index case is doubled in early-onset (age 52 or less) cases while no correspondingly increased risk is associated with later-onset cases. Twin studies are especially valuable in differentiating environmental from genetic transmission, even though they do not eliminate the problem. The concordance rate for CHD is higher in monozygotic than in diziygotic twins of the same sex, indicating that a genetic factor is involved[10]; when the twins are of unlike sex, concordance is very high if the index case is female[10]. The latter finding again points toward a strong genetic element because a women who breaks through the barrier of her relative protection against CHD must, presumably, have a strong hereditary predisposition.

Table 1. Cumulative probability of fatal coronary heart disease (%) before age 60

	Probands with:			Reference Persons
	Fatal myocardial infarction (MI)	Non-fatal MI	Angina Pectoris	
Brothers	34.5%	28.9%	15.4%	4.4%
Sisters	8.2%	3.5%	-	-

After Rissanen, Brit. Heart J. 42:294, 1979

Table 2. Parents of probands: Cumulative probability of dying (%) from coronary heart disease by age 70

Age of Proband at first myocardial infarction	FATHER		MOTHER	
	South Finland	East Finland	South Finland	East Finland
≤ 45	43.3	52.3	35.8	24.9
46-50	29.5	35.9	14.5	11.3
51-55	12.1	20.2	6.7	13.2
Reference Group	9.4	7.6	10.0	7.4

After Rissanen, Am. J. Cardiol. July 1979

Familial Resemblance in Risk Factors

Accepting the fact that relatives of CHD patients carry themselves a higher risk of CHD, at least if the disease presents relatively early in life in the proband, the question arises whether this increased risk is due to the further fact that elevated risk factors are more common both in the probands and their relatives because of familial resemblance in risk factors. How strong is this resemblance? There is a rule that rare, single genes show strong familial aggregations while common, polygenic traits are associated with weaker resemblance amongst relatives. The familial hyperlipidaemias illustrate this generalization. If risk factors like serum cholesterol or blood pressure are viewed as continuous variables, as they should be, there is familial resemblance along the whole range but the correlation coefficients between siblings or parents and children, though significant, are not high and of the order of, perhaps, 0.15-0.25[11-13]. Against this background, it may now be asked to what extent the presence of a major risk factor in a CHD

proband affects CHD risk in a close relative and what proportion of this risk may be mediated by one or more of these risk factors.

The Role of Risk Factors in Mediating Familial Coronary Heart Disease Risk

The presence of hyperlipoproteinaemia in an index patient with CHD increases CHD risk in a first degree relative[14] (Table 3). The risk is relatively greater in younger relatives and younger index patients transmit higher risk even with "normal" lipid levels, remembering that "normal" in this analysis is really a misnomer, meaning merely that no Type II or IV hyperlipoproteinaemia is present. More recently, the increased CHD risk of Type II relatives of probands with Type II hyperlipoproteinaemia has again been well documented[15].

Another study in Finland[16] (Table 4) shows not only that hypertension and hypercholesterolaemia are much more common in a CHD proband with a CHD family history but that the same traits are also a great deal more frequent in his siblings (no such relationship exists for hypertriglyceridaemia). On the basis of these data, the authors believe that the two risk factors must largely account for familial clustering of CHD. Data from the Tromsø Study, however, do not bear out this conclusion since risk factors do not differ amongst persons with and without a family history of CHD[17] (Table 5).

Before proceeding, attention should be drawn to studies which address the question whether risk factor levels in childhood bear a relationship to the presence or absence of a family history of CHD in their adult relatives. When schoolchildren are divided into those whose serum cholesterol levels are in the highest and lowest 5% of the distribution and the rest with levels in between, myocardial infarction is more common in the male and female relatives of the children in the top range[18]. However, in another study, taking as point of departure schoolchildren with and without a parental history of CHD, average serum cholesterol levels did not differ but triglycerides were higher and HDL-cholesterol levels lower in children of CHD patients than controls[19]. Yet, as a rule, hypercholesterolaemia is common amongst children of young patients with CHD[20].

Why does Coronary Heart Disease aggregate in Families?

It may be tentatively concluded, up to this point, that at least part of the reason why CHD clusters in families lies in the fact that relatives of CHD probands are more often hyperlipidaemic or hypertensive than people in the population at large. How much of the clustering, however, remains unexplained? A number of years ago, it was suggested, using a model based on existing epidemi-

Table 3. Increased Risk of Death to first-degree Relatives of Patients with Coronary Heart Disease

Index Patients	First Degree Relatives	
	All Relatives	"Younger Relatives"
Whole Group	x 1.5*	x 2.5**
"Younger", with normal lipids	x 1.9*	x 2.4**
Type II Hyperlipoproteinaemia	x 2.5**	x 4.9**
Type IV "	x 1.9	x 4.4**
Spouses with normal lipids	x 0.9	x 0.9

* $p < 0.05 > 0.01$

** $p < 0.01 > 0.001$

After Patterson and Slack, 1972

"Younger" means < 55 years for men and < 65 years for women.

Table 4. Frequency of Hypertension and Hyperlipidaemia in case sibs according to parental history of Coronary Heart Disease (CHD)

	HYPERTENSION %			HYPERCHOLESTEROLAEMIA %			HYPERTRIGLYZERIDAEMIA** %		
	Proband	Brothers	Sisters	Proband	Brothers	Sisters	Proband	Brothers	Sisters
Mother died of CHD before age 70 (14 families)	70.0	37.5	43.8	60.0	45.8	21.9	10.0	20.1	18.8
Father died of CHD before age 70 (38 families)	56.2	29.9	26.9	26.1	17.9	22.4	30.4	19.4	17.1
Neither parent died of CHD before age 70 (108 families)	33.3	16.4	23.6	30.6	21.4	13.5	26.4	15.7	22.5

After Rissanen and Nikkila, Brit. Heart J. 42:373, 1979

* age-adjusted serum cholesterol $\geq$ 8.8 mmol/l (men and women)

** age-adjusted serum triglyzerides $\geq$ 2.3 mmol/l (men); $\geq$ 1,7 mmol/l (women)

ological data, that this fraction might be substantial[4]. Quite recently, in a retrospective study, it was concluded that the family history discriminated much more strongly between CHD patients and matched controls than any other of a large series of risk factors measured[21]. In the first prospective study where the family history of CHD was included in multivariate analysis comprising all the other major risk factors, it emerged as an independent predictor as far as CHD in the father though not the mother was concerned[22].

Table 5. Age-adjusted mean values of Coronary Heart Disease risk factors in subjects with and without myocardial infarction (MI) among their first degree relatives

The Finnmark Study (Tromsø)

	MALES		FEMALES	
	MI	No MI	MI	No MI
Cholesterol (mg/dl)	275.0	265.7	264.0	260.5
Triglyzerides (mmol/l)	2.20	2.15	1.56	1.58
Syst. B.P. Pressure	138.1	134.8	122.9	124.6
Diast. B.P. Pressure	81.8	80.7	75.9	76.1
Rel. Body Weight	2.4	2.4	2.3	2.3
Daily No. Cigarettes/ person	8.3	8.8	5.6	4.7

After Thelle and Førde, Am. J. Epidemiol. 110:708, 1979

N.B.: In the "Tromsø Study", the relative risk for MI in first degree relatives of MI patients ranged from 5.5 to 12.8, depending on the sex of the patient.

The latest contribution to the question raised comes from the Framingham Study[22]. It is based on a 26-year follow-up period and uses, for the first time, clinical-epidemiological diagnoses of CHD as evidence for a positive family history rather than a hearsay report from a family member with all its sources of unreliability. For pairs of brothers who were both examined, the occurrence of CHD in an older brother was a significant predictor of CHD in his younger brother, even when age, blood pressure, serum cholesterol, smoking and relative weight were taken into account by multivariate analysis. The excessive risk carried by a positive history is 1½ to 2-fold but the analysis does not permit a statement how much of this excess is referable to the family history alone. The proportion cannot be large in absolute terms and it must be remembered that most of the CHD probands in the Framingham cohort are middle-aged or older.

Summary and Conclusion

Viewing the evidence presented in broad perspective, a family history of CHD in a close relative emerges as a CHD risk factor, partly independent of the concurrent risks carried by others like elevated levels of blood pressure, serum cholesterol and smoking. The risk inherent in a positive family history appears to be largely but not entirely limited to the familial occurrence of early-onset CHD. It is not known what risk factors other than those mentioned might contribute to the familial clustering of CHD, remembering that familial resemblance in risk factors might be determined by genetic factors, shared environmental influences or both; they range from mechanisms related to thrombosis-haemostasis to the risks

associated with various types of psychosocial stress. Genetic predispositions mediated through the immune system, reflected by HLA-patterns, or indicated by markers like the blood groups must also be kept in mind. It is likely that further systematic studies of CHD and risk factors in families selected from the population or special target groups will bring new insights into the mechanisms of atherosclerosis and its clinical consequences.

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