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FAMILIAL HYPERCHOLESTEROLAEMIA (FH)

Report of a second WHO Consultation

Geneva, 4 September 1998

This report is dedicated to the memory of
Professor Roger R. Williams, founder and first chairman
of the International MED-PED FH Organization

World Health Organization
Human Genetics Programme
Geneva, 1999

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1. Introduction

It is estimated that about 250 million persons in the world are exposed to a very high risk of dying at young age because they carry one or more genes that promote inherited lipid disorders. These disorders include Familial Hypercholesterolemia (FH, estimate 10 million), Familial Combined Hyperlipidemia (FCH, estimate 40 million) and severe Polygenic Hypercholesterolemia (PH, estimate 200 million).

FH is a disorder of cholesterol metabolism with an autosomal dominant mode of inheritance. This disorder is caused by mutations in the gene that encodes the low-density lipoprotein (LDL) receptor, a protein that maintains cholesterol homeostasis. FH can be diagnosed by evident physical and clinical signs but also by demonstration of mutations in the LDL-receptor gene. The molecular basis of FCH and PH has not been elucidated yet. As FH, FCH is also an autosomal dominant disorder caused, in all likelihood, by a combination of several genes. PH is a disorder with less evident inherited characteristics, and is strongly modulated by environmental factors.
Modern effective medication can now normalise lipid levels in persons affected with these disorders. The results of recent very large clinical trials have demonstrated that the use of such medication can prevent early, fatal and non-fatal myocardial infractions and stroke and can prolong high-quality life for many decades [1-5].

Unfortunately, recent surveys have also shown that the majority of persons affected with these treatable disorders are undiagnosed, untreated or poorly treated. Without identification and further intervention, most of them will die at ages of 35 to 65 years. However, with early diagnosis and treatment, they can live longer and more productive lives without heart attacks. Physicians and scientists from 33 countries, feel a growing social conscience to prevent these needless heart attacks at young age [6]. By working together in the MED-PED program, **M**ake **E**arly **D**iagnoses to **P**revent **E**arly **D**eaths, a strong effort to identify and treat affected persons in order to control the deadly consequences of these diseases, can be achieved. Initial efforts are focused on the most severe and genetically best understood disorder: Familial Hypercholesterolemia.

In the recently published report of a WHO Consultation on FH, practical steps were described for improved identification, treatment and long-term follow-up of persons with FH [6]. These steps can be used to form the basis of a structured organisation dedicated to the control of inherited lipid disorders on a national level:

1 Identification of index cases with known or suspected FH
2 Contacting relatives to find other persons needing testing and treatment for FH
3 Creation of a registry of FH patients and their physicians
4 Education of patients and physicians with regard to optimal treatment
5 Connection of lipid specialists with primary care physicians and patients
6 Connection of cardiologists with primary care physicians and patients
7 Follow up contacts to promote optimal control and compliance
8 Organisation of lay and patient associations
9 Involvement and support of government health agencies and insurance companies
10 Co-ordination and promotion of research on inherited lipid disorders

With great progress being made in understanding genetic factors promoting common diseases such as inherited lipid disorders, the time has now arrived for co-ordinated practical efforts to apply the information currently available in order to control a serious health hazard on a global level. FH will serve as a model for future efforts to control other inherited lipid disorders and other treatable inherited diseases. Where the first report of a consultation by the WHO on FH in Paris in October 1997 described the disease and the associated cardiovascular risk [6] , this second report inventories the actual situation with regard to the extend of the burden towards public health in the countries participating in the International MED-PED FH program. The second report is based on a consultation organised by the WHO in September 1998 in Geneva.

2. What is MED-PED ?

MED-PED is a humanitarian program to find and help persons with inherited high cholesterol. Collaborators participating in this program are dedicated to identifying persons at high risk for myocardial infarctions or premature death and to scientific and clinical research in the field of inherited lipid disorders with the aim to improve medical treatment. There are no commercial interest associated with MED-PED. Expenses generated by MED-PED activities are always covered by the individual collaborator's own budget, but financial support from other sources may be accepted as unrestricted research grants.

MED-PED collaborators were invited to supply data on the situation of inherited lipid disorders in their country during a first consultation in September 1998 organised by the WHO. MED-PED collaborators were also invited to give a short description of the current MED-PED activities in their country. Reactions to this varied from short descriptive information to more lengthy general overviews. Most participating countries responded to the request for information. This survey, lastly updated in February and March of 1999, addressed the extent of identification and methods used, diagnosis and treatment of inherited lipid disorders and government involvement. Should more specific or detailed information be required, the MED-PED collaborator in question or the Co-ordinating Centre can be contacted.

It is the intention that this report will serve as a basis from which targeted implementation of the active case-finding of inherited lipid disorders can be initiated on a global level.

Countries participating in the MED-PED Program (by August 1999)

Australia	Hungary	Poland
Austria	Iceland	Portugal
Brazil	Ireland	Russia
Canada	Israel	Singapore
Chile	Italy	Slovenia
China (Hong Kong, A.R.)	Japan	South Africa
Colombia	Lebanon	Spain
Czech Republic	Malaysia	Sweden
Denmark	Netherlands	Switzerland
France	New Zealand	United Kingdom
Germany	Norway	USA
Greece		

International MED-PED FH Steering Committee includes Dr. Paul Hopkins, Salt Lake City, USA, co-chair; Dr. Joep Defesche, Amsterdam, the Netherlands, co-chair; Professor Ulrike Beiseigel, Hamburg, Germany; Professor John Betteridge, London, United Kingdom; Dr. José Ernesto Dos Santos, Ribeirão Preto, Brazil; Professor Ole Faergeman, Aarhus, Denmark; Dr. Ian Hamilton Craig, Adelaide, Australia; Professor Michael Hayden, Vancouver, Canada; Dr. John Kastelein, Amsterdam, the Netherlands; Dr. Leiv Ose, Oslo, Norway.

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3. Numbers of patients with inherited lipid disorders throughout the world

MED-PED collaborators were asked to estimated the number of patients with Familial Hypercholesterolemia (FH), Familial Combined Hyperlipidemia (FCH) and Polygenic Hypercholesterolemia (PH). When accurate estimates were not available, the generally accepted incidences of 0.2% for FH, 2% for FCH and 3% for PH were used. To assess the situation with regard to identification and treatment of persons with FH, it was estimated what percentage of FH patients is momentarily identified, and which part of these is on therapy with HMG CoA reductase inhibitors, or statins, and in what percentage the disorder is well controlled. Well controlled being defined as a total cholesterol level below 240 mg/dl or 6.2 mmol/l and a LDL-cholesterol level below 130 mg/dl or 3.4 mmol/l.

One has to bear in mind that in principle, each country has its own distribution of cholesterol levels, and hence, the extent of cardiovascular risk associated with hypercholesterolemia may vary when hypercholesterolemia is defined as cholesterol levels over the 95th percentile for gender and age.

In Tables 1 to 3 these data are summarised by continent. The estimated incidences of inherited lipid disorders seem to be correct for most countries. Incidences below or over 5.2% may be explained by different genetic background or ethnic variation in the various countries.

This report confirms that the circumstances of FH is a matter of grave concern. The highest estimate of patients identified is 50%, but only a portion of these is receiving statin therapy and fewer are well-controlled. In the best case scenario, this would mean that a maximum of 25% of all FH patients is adequately treated. This is the case in Iceland, the country with the smallest population and therefore the smallest number of FH patients.

The highest degree of identification and optimal control of patients with FH is found in some western European countries, while the lowest degree is present in countries belonging to the Pacific continent or east Europe. It is remarkable that even with a relative high degree of identification, health care measures to reach optimal control of this life-threatening disorder lag behind, since the percentage of well-controlled FH patients never exceeds 50% in all countries (except Sweden with 60%).

It is evident that for the improvement in the situation for patients with FH many actions have to be undertaken: a higher degree of identification, availability of effective cholesterol-lowering medication and the insurance of long-term follow-up and drug compliance. Governments and the different public health systems should take measures to increase the awareness among the general public and medical community about the extend of the health hazards associated with inherited lipid disorders. It is on this level where the initiative must be taken and public awareness actively should be promoted. Subsequently, the medical and scientific communities and insurance companies must be prepared to follow up on these actions and must be prepared to take care of the special needs of persons with inherited lipid disorders.

Table 1: Europe: expected prevalence of inherited lipid disorders and extend of diagnosis and treatment of FH

country	total population	patients with FH	patients with FCH	patients with PH	total% with lipid disorder	%FH diagnosed	%FH on statins	%FH well controlled	
Austria	7.5 million	15 000	15 000	250 000	3.7	25-49	10-24	25-49	
Czech Republic	10.4 million	20 600	200 000	200 000	4.0	5	5-8	4-5	
Denmark	5.2 million	10 400	104 000	156 000	5.2	10	10	10	
France	58 million	116 000	1 160 000	1 740 000	5.2	25-49	25-49	10-24	
Germany	80 million	160 000	1 600 000	2 400 000	5.2	<10	60-80	30-50	
Greece	10 million	20 000	200 000	300 000	5.2	not known	<50	20-30	
Iceland	270 000	540	5 400	8 100	5.2	44	80	35-40	
Israel	6 million	12 000	120 000	180 000	5.2	<10	<10	<10	
Italy	57 million	120 000	1 200 000	1 600 000	4.0	35	60	40	
Netherlands	15.5 million	40 000	310 000	465 000	5.3	20	90	75	
Norway	4.5 million	18 000	90 000	180 000	6.4	2-25	15-20	25	
Poland	38.6 million	77 200	772 000	1 158 000	5.2	<10	<10	10	
Russia	150 million	300 000	3 000 000	4 500 000	5.2	<1	<1	not known	
Slovenia	2 million	4 000	40 000	100 000	7.2	7-8	7	3-4	
Spain	40 million	80 000	600 000	800 000	3.7	<25	80	40-50	
Sweden	9 million	18 000	50 000	75 000	1.6	30	25	60	
Switzerland	7 million	47 300	140 000	210 000	5.7	10-24	10-24	10-24	
United Kingdom	55 million	110 000	1 100 000	1 650 000	5.2	10	10	10%	

Table 2: North and South America: expected number of patients with inherited lipid disorders and extend of diagnosis and treatment of FH

country	total population	patients with FH	patients with FCH	patients with PH	% with lipid disorder	%FH diagnosed	%FH on statins	%FH well controlled	
Brazil	160 million	320 000	3 200 000	4 800 000	5.2	<10	<10	<10	
Canada	30 million	60 000	600 000	900 000	5.2	15	39	22	
Canada, Quebec	8.9 million	28 926	38 000	57 000	1.4	10-24	25-49	10-24	
U.S.A	258 million	516 000	5 160 000	7 740 000	5.2	<10	<10	<10	

Table 3: Asia, Africa and Pacific: expected number of patients with inherited lipid disorders and extend of diagnosis and treatment of FH

country	total population	patients with FH	patients with FCH	patients with PH	% with lipid disorder	%FH diagnosed	%FH on statins	%FH well controlled	
Australia	15 million	30 000	300 000	450 000	5.2	<2	>95	<50	
Hong Kong	6.5 million	13 000	130 000	195 000	5.2	4	3	1	
Japan	120 million	240 000	1 200 000	1 200 000	2.2	10	100	30	
New Zealand	3.8 million	7 600	11 400	38 000	1.5	<1	80	46	
Singapore	3.4 million	6 800	68 000	102 000	5.2	3	90	<10	
South Africa	40 million	120 000	800 000	120 000	2.6	<10	<10	<10	

4. Case-finding and registration of persons with FH

The percentage of cardiologists and general practitioners that actively screen their patients for inherited lipid disorders or perform aimed case-finding never exceeds 30% (Table 4). Taking into account that most higher screening intensities only take place regionally, it is realistic to conclude that in most countries the percentage of cardiology and general practices that are involved in screening is well below 10%.

This situation is far from ideal. Cardiology practices are sites with a clustering of inherited lipid disorder patients and general practices usually have good access to families. Thus, the cardiologist and the family physician should form the basis of screening and case-finding: index cases identified by the cardiologist and subsequent family investigation by the family physician with the referral to a Lipid Clinic or a lipid specialist in cases of a suspected inherited lipid disorder. Unfortunately, this is hardly the case. Lack of specialised knowledge with regard to these disorders is probably the main reason that the chain of logical and necessary events fails: diagnosis→family investigation→case finding→treatment→prevention, is delayed already at the beginning.

There is however a strong tendency to register patients as soon as they are identified. Table 4 shows the percentage of patients on statin therapy and the percentage followed up after identification and registration. It is clear that registration of patients enhances the quality of treatment and the follow-up.

Inherited lipid disorders are by far the most common forms of genetic disease. Unfortunately, this notion is not perceived by many health professionals. Simple adaptations in the educational and (post-graduate) training programs of health professionals may result in the desired intensification of family-screening in medical practice.

Table 4: Case-finding and registration

country	% cardiologist that screen	% GP that screen	type of FH registry	region served	# FH patients in registry	% FH patients registered	% on statins	% follow-up
Australia	<10	<5	comp	entire country	538	<2	>95	50
Austria	10-24	10-24	comp	entire country	1388	<10	50-89	10-24
Brazil	<30	<10	comp	regional	65	<1	60	90
Canada, B.C.	<10	<10	comp	B.C.	1279	<10	39	30
Canada, Ont.	<10	<10	comp	entire country	2260	<10	95	95
Canada, Quebec	<10	<10	comp	local, Quebec	1615	<10	98	>95
Czech Republic	<1	1	comp	entire country	263	25	77	0
Denmark	<1	<1	comp, thl	entire country	nd	10	80	80
France	<10	10-24	comp	Paris Lipid Clinic	177	<10	>90	>90
Germany	<10	<15	comp	entire country	1608	<25	>90	90
Greece	<50	<25	none	na	na	na	na	na
Hong Kong	0	5	comp	entire country	nd	nd	nd	nd
Iceland	<10	<10	comp	entire country	239	>90	>90	>90
Israel	<10	<10	comp	entire country	560	<10	nd	nd
Italy	15	10	thl	entire country	1300	10	60	50
Japan	<10	<5	comp	nd	300	80	70	70
Netherlands	<10	<10	comp	entire country	7536	>90	>90	>90
New Zealand	30	5	thl	Dunedin, Christchurch	113	nd	80	100
Norway	5	10-20	comp	entire country	1781	75-80	>90	>90
Poland	10-24	10-24	comp	northern Poland	42	<10	90	90
Russia	0	0	comp, thl	St. Petersburg	230	100	10	75
Singapore	5	5	thl	Singapore Lipid Clinic	54	25	100	100
Slovenia	10-15	10	none	na	na	na	na	na
Spain	<10	<10	thl	nd	<1	nd	nd	nd
South Africa	<10	10-24	comp	Western Cape	3450	3	50-89	50-89
Sweden	5	10	comp, thl	Stockholm	300	8	>90	>90
Switzerland	10-24	<10	comp	entire country	1219	<10	>90	<10
U.K.	<10	<10	comp	entire country	3000	3	>90	15
U.S.A.	<10	<10	comp	entire country	6919	<10	50-89	>90

comp: computer registry; thl: typed or hand written lists; nd: no data available; na: not applicable.

5. Patient care

Once patients have been identified, they enter a level of health care which is not really suited for their needs. Table 5 summarises the situation with regard to patient care and follow-up. Although statin medication is available in all countries, patients do not have unrestricted access to these medications. In many instances the costs for these drugs are not fully reimbursed, or there is even no reimbursement at all. These differences in reimbursements between countries or the partial reimbursements within countries can be attributed to differences in private health insurance policies but also to different national or regional governmental health regulations. Primary prevention of the clinical manifestations of atherosclerosis is still a controversial issue. Uncontrollable rise in health care costs is feared to result from prescribing cholesterol lowering drugs on a large scale. On the other hand, fairly accurate estimates of the costs of primary prevention can be made [7-16], and when compared to the total costs incurred from cardiovascular disease on a national level (in terms of hospitalisation, economical loses etc.) [17], primary prevention is favourable (Table 6). Thus, full reimbursement of medication cost, would in all likelihood, not only save lives, but also money.

Concerning the education of patients and physicians, the situation seems to be improving. In most countries patients are educated with regard to the use of medication, adaptation of life-style and drug compliance by means of brochures, books and special meetings. Some MED-PED collaborators manage to raise public awareness with media publicity in the form of articles in national newspapers or television broadcasts. To a somewhat lesser extent, special attention is paid to specific training of physicians with regard to identification and treatment of inherited lipid disorders. Pharmaceutical companies can fulfil an important task in the education of the medical community by means of speciality meetings. Also, patient organisations can play a crucial role in raising public awareness and promotion of the patient's interest towards government involvement. Unfortunately, active patient organisations are present only in a few countries.

In dealing with the management of inherited lipid disorders, the influence and support provided by governments is only minor. Governments participation is mostly restricted to payment of blood cholesterol testing, although some follow-up actions are emerging. Small pilot studies are being initiated to address lipid specialist networking, long-term drug compliance, case-finding or DNA-testing of FH. Only the Netherlands government provides support with a large pilot study for FH case-finding. It is expected that by the year 2000, the Dutch government will implement FH case-finding on a large national scale, with the aim to identify every FH patient within the next 5 to 8 years

Table 5: Patient care: medication, reimbursement of costs, involvement of government and support, actions to educate patients and physicians

country	statins available	patients obtaining 80% of costs reimb.	formal patient education	physician education	active patient organisation	government support
Australia	A, C, F, P, S	85% of cases	yes	yes	no	reimbursement of office visits and pathology testing
Austria	A, C, F, L, P, S	>90% of cases	yes	yes	no	pilot of long term compliance
Brazil	A, C, F, L, P, S	none	yes	yes	no	none
Canada, B.C.	A, F, L, P, S	not known	yes	yes	no	blood tests
Canada, Ont.	A, C, F, L, P, S	in 60% of cases	no	no	yes	none
Canada, Que.	A, C, F, L, P, S	>90% of cases	yes	yes	yes	blood tests, networking
Czech Republic	A, F, L, P, S	all cases	yes	yes	no	small pilot for DNA testing
Denmark	A, C, F, L, P, S	75% of costs reimb.	yes	yes	no	small pilot for DNA testing
France	A, C, F, P, S	>90% of cases	yes	yes	no	blood tests, small pilot DNA testing
Germany	A, C, F, L, P, S	in 50% of cases	yes	yes	no	none
Greece	A, F, L, P, S	<50% of cases	no	no	yes	none
Hong Kong*	A, F, L, P, S	in 75% of cases	yes	no	no	none
Iceland	A, F, L, P, S	>80% of cases	yes	no	no	blood tests
Israel	A, C, F, L, P, S	50 to 90% of cases	yes	yes	no	none
Italy	A, C, F, P, S	75%	yes	yes	yes	none
Japan	A, C, F, L, P, S	all cases	yes	yes	no	blood tests, networking
Netherlands	A, C, F, P, S	all cases	yes	yes	yes	large pilots of FH and FCH case-finding
New Zealand	A, C, F, P, S	in 70% of cases	yes	no	yes	none
Norway	A, C, F, L, P, S	>90% of cases	yes	yes	no	none
Poland	A, C, F, L, P, S	in 70% of cases	yes	yes	yes	none
Russia	F, L, P, S	none	yes	no	no	supports FH case-finding
Singapore	A, C, F, L, P, S	none	yes	yes	no	none
Slovenia	C, F, L, S	all cases	no	no	no	blood tests, educating physicians
Spain	A, C, F, L, P, S	none	yes	yes	yes	none
South Africa	A, C, F, P, S	<10% of cases	yes	yes	no	none
Sweden	A, C, F, P, S	none	yes	yes	no	none
Switzerland	A, C, F, P, S	all cases	yes	yes	no	none
U.K.	A, C, F, P, S	all cases	yes	yes	yes	none
U.S.A.	A, C, F, L, P, S	10 to 24% of cases	yes	yes	yes	none

A: atorvastatin; C: cerivastatin; F: fluvastatin; L: lovastatin; P: pravastatin; S: simvastatin

*Hong Kong, Special Administrative Region, China

Table 6: Approximate costs (in USD) per life year saved (lys) by lowering cholesterol with statin medication as primary prevention in men and women, 45 years old [7-16]

Country	men	women	total per lys in billions*	total costs for cardiovascular disease in 1985 in billions [17]
Canada	17 000	27 000	1.32	5.06
Czech Republic	7 000	17 000		
France	7 000	17 000	1.39	12.85
Germany (West)				14.42
Hong Kong	7 000	27 000		
Iceland	17 000	17 000		
Italy				10.72
Japan	17 000	27 000	5.28	23.17
Netherlands	7 000	17 000		
Norway	7 000	17 000		
Singapore	7 000	17 000		
Slovenia	7 000	17 000		
Spain	7 000	17 000	0.96	23.17
South Africa	1 700	2 700		
U.K.				13.44
U.S.A.	7 000	17 000	6.19	64.02

*: total costs per life year saved were calculated from the estimated number of FH patients present (table 1 -3) and the approximate costs per life year saved by lowering cholesterol with statin medication as primary prevention in men and women, 45 years old. Approximate costs categories were derived from references 7 to 16.

6. Advanced method for the identification of patients with inherited hypercholesterolemia.

Disorders which to screen

It is quite evident that a screening program can only be successful when those individuals identified as carriers of the disorder can be offered effective treatment. Cardiovascular disease is still the leading cause of death in most countries. The majority of risk factors contributing to cardiovascular disease have been identified and treatment is often available. Premature cardiovascular disease is associated with many hereditary disorders. Examples include Familial Hypercholesterolemia, hypertension, diabetes and hyperhomocysteinemia. In many of these cases the molecular basis of the disorder is not yet fully understood, or the association with premature cardiovascular disease is not straightforward. An exception is Familial Hypercholesterolemia (FH). The aetiology of FH is completely understood and it is generally accepted that persons with FH are exposed to the highest possible risk for the development of premature cardiovascular disease. Furthermore, the molecular basis of the disorder has been elucidated. Effective treatment of hypercholesterolemia, resulting in substantial reduction of the risk of premature atherosclerotic complications, is available. In fact, FH is one of the few genetic disorders which meet all conditions for large scale screening programs (Table 7).

Table 7:
Criteria worthwhile for large scale screening program for health hazard conditions [18].

1.	The condition should be recognisable at a latent or early symptomatic stage.
2.	The natural history of the condition should be understood.
3.	The condition must be considered to be an important health hazard.
4.	A suitable diagnostic test should be available.
5.	The diagnostic test should be acceptable.
6.	The cost of case finding should be economically balanced.
7.	Facilities for diagnosis and treatment should be available.
8.	There should be consensus on whom to treat as patient.
9.	Acceptable treatment for patients with recognised disease should be available.
10.	Case finding should be an ongoing process.

Familial Hypercholesterolemia (FH)

FH is an autosomal dominant disorder of lipoprotein metabolism with a penetrance of almost 100%, meaning that half of the offspring of an affected parent has a severely elevated plasma cholesterol level from birth onwards, with males and females equally affected [19].The premature atherosclerosis in patients with FH is for the greatest part accounted for by the elevated low-density lipoprotein (LDL) fraction in plasma. These cholesterol-rich lipoprotein particles are under normal circumstances cleared by the liver via LDL-receptor mediated endocytosis. The underlying cause for FH are mutations at the LDL-receptor locus, impairing LDL-receptor function [19]. Cardiovascular disease becomes manifest in more than 50% of male and female patients with FH before 55 years of age [20]. Moreover, total mortality by coronary artery disease is many times greater for male and female patients with FH, between 20 and 39 years of age, than for unaffected persons in that age group [21].

The clinical diagnosis of FH is based on typical physical signs, laboratory findings and the patient's history. The hallmark of the disease is an increased total- and LDL-cholesterol level, above the 95th percentile for sex and age, with high-density lipoprotein (HDL), very low-density lipoprotein-cholesterol (VLDL) and triglycerides usually in the normal range. Total plasma cholesterol levels in FH heterozygotes vary between 7.5 and 13 mmol/l (290 and 500 mg/dl) and FH homozygotes have levels between 16 and 26 mmol/l (600 and 1000 mg/dl).

Increased LDL-cholesterol levels often result in cholesterol deposits, which can be easily recognised as xanthomas on the Achilles tendons and extensor tendons of hands and feet, and to a lesser extent on the knees and elbows. Very obvious clinical signs are xanthelasmas on the eyelids and an arcus cornealis: a white deposit of lipids in the outer rim of the iris.

While the xanthomas are pathognomic for FH, the xanthelasmas and arcus cornealis are not. Xanthelasmas may be present in normolipidemic persons, and appear more frequently in older persons. Also an arcus can often be seen in persons over

60 years of age and is than called an arcus senilis. FH is sometimes difficult to differentiate from hypercholesterolemias of other origin, such as familial combined hyperlipidemia or polygenic hypercholesterolemia. The clinical characteristics, as described before, may facilitate the diagnosis. By weighing the occurrence of these clinical signs, alone or in combination with others, a diagnostic scoring table can be constructed for FH (Table 8).

Table 8: Diagnostic scoring table for FH (constructed by the Dutch Lipid Clinic Network)

Family history			
a	First degree relative known with premature (men<55 yrs, women <60yrs) coronary and vascular disease.		1
b	First degree relative known with LDL-cholesterol >95th percentile.		
	and/or		
a	First degree relative with tendon xanthomata and/or arcus cornealis.		2
b	Children below 18 yrs. with LDL-cholesterol >95th percentile.		
Clinical history			
a	Patient has premature (men<55 yrs, women <60yrs) CAD		2
b	Patient has premature (men<55 yrs, women <60yrs) cerebral or peripheral vascular disease.		1
Physical examination			
a	Tendon xanthomata		6
b	Arcus cornealis below the age of 45 yrs.		4
Laboratory analysis			
		mmol/l	mg/dl
a	LDL-cholesterol	>8.5	>330	8
b	LDL-cholesterol	6.5 - 8.4	250-329	5
c	LDL-cholesterol	5.0 - 6.4	190-249	3
d	LDL-cholesterol	4.0 - 4.9	155-189	1
	(HDL-cholesterol and triglycerides are normal)			
DNA-analysis				
a	Functional mutation low-density lipoprotein receptor gene present			8

Diagnosis of FH is:

certain when	>8 points
probable when	6-8 points
possible when	3-5 points

Modern cholesterol-lowering therapy with hydroxy-methyl-glutaryl Co-enzyme A (HMG CoA) reductase inhibitors has been proven to lower LDL-cholesterol levels in hypercholesterolemic patients [1-5]. A prospective clinical trial in patients with FH, using quantitative computer assisted angiography of the coronary arteries, has demonstrated that lowering LDL-cholesterol levels can arrest the progression of coronary atherosclerosis and in some cases can induce regression [22].

Selective screening of four general practices in a middle-sized town with a population representative for the Netherlands, has not only shown that the prevalence of FH in the Netherlands was very close to one in 400 persons, but also that only a minority (<10%) of FH patients was diagnosed as such and treated accordingly [23]. By extrapolation of these figures to the general Dutch population, the total number of heterozygous FH patients present in the Netherlands would exceed 40,000, while only 2000 to 3000 of these were receiving proper medical care at that time. Given the fact that persons with FH are exposed to the highest risk of dying from the complications of coronary atherosclerosis, that

the disorder has a high prevalence in the general population, the majority of patients has not been identified and is consequently not under adequate treatment, these persons with FH should be identified with the utmost priority, since effective and safe treatment is available.

Method of screening

There are three basic requirements for implementation of a large-scale screening program:

1. An unequivocal diagnosis of the disorder, under scrutiny, should be available. Demonstration of an underlying defect in a gene, leading to the disease, constitutes in fact the definite confirmation of the diagnosis. Each genetic disorder separately is relatively rare in the general population, unless a founder mutation is present. When attempting to identify persons with such a genetic order, it is obvious that selection of high-risk groups in the general population is a far better approach. The family members of a patient with a definitely diagnosed genetic disorder constitute such a high-risk group. Examination of family members of such an index-patient will yield a number of persons with the same disorder.

2. Facilities to identify and locate these high-risk groups, i.e. families of index-patients should be available. In this component, an active and direct approach of index-patients and their family members is essential. For this purpose, nurses (referred to as genetic field workers) trained in performing family studies and instructed to supply relevant information to persons involved, should be employed.

3. After early recognition, effective treatment which is likely to result in the prevention of premature death or disease, should be offered. When a nation-wide screening program is initiated, centres for referral should be present.

Screening for persons at risk for premature cardiovascular disease, using FH as a model

In the Netherlands the three basic requirements for identification of persons with FH have been established. An accurate and reliable diagnostic procedure to determine LDL-receptor gene defects, the underlying cause of FH, is available. For the 110 characterised LDL-receptor gene mutations, known to be present in the Netherlands, detection assays based on the polymerase chain reaction (PCR) technique, have been developed [24]. Furthermore, an organisation for identification and localisation of index-patients and their family members throughout the country has been set up. By employing a number of genetic field workers, this organisation acts as a co-ordinating centre and as an intermediate between the DNA-diagnostic laboratory, the identified patients and the centres for referral. The centres for referral are organised in a nation-wide network of specialised Lipid Clinics.

Identification of index cases

The Amsterdam Lipid Research Clinic at the Academic Medical Centre of the University of Amsterdam and at the Slotervaart University Teaching Hospital is responsible for the medical management of a large cohort of patients, specifically referred for diagnosis and treatment of disorders of lipoprotein metabolism. This cohort comprises a group of approximately 2500 personswith a clinical diagnosis of FH. DNA samples of these FH patients are routinely analysed for the presence of LDL receptor gene mutations known to be present in the Netherlands, using the PCR-based assays. In Dutch patients with FH, more than 100 different LDL-receptor gene mutations have been identified. These mutations account for approx. 80% of FH cases in the Netherlands [25]. Once a mutation has been identified in a patient with the clinical diagnosis FH, this patient is referred to as an index-case.

Family investigation by genetic field work
After informing the referring physician and obtaining approval to approach the patient, index cases are contacted via telephone by the genetic field worker (GFW), to explain the purpose of the identification program. The index-case is provided with an information brochure, describing the nature of the disease and the procedure followed in the identification program. When written consent is given to participate in the program, the GFW arranges a house visit, requesting to assemble as many family members as possible: parents, children, brothers, sisters, uncles, aunts and cousins. When such a house call and family gathering is arranged, the GFW visits the family on location. For each family member present, a health questionnaire is filled out, providing demographic data, medical history and family relations: names and addresses of family members who may be contacted at a later moment. At the same time a blood sample is drawn from each family member present. Written and signed

informed consent is obtained from all persons willing to participate in the program. Blood samples are analysed for the presence of the mutation causing FH in the index case. The information obtained through the health questionnaires is recorded in a computerised data base, and the information on family relationships is condensed in a family tree. When the amount of information allows, the family tree is expanded, and after more family members are contacted, the same procedure is repeated.

Reporting results and referrals
Relatives, shown to be carrier of the mutation causing FH in the family, are informed of the findings of DNA analysis in writing, and are strongly advised to visit a physician in a specialised Lipid Clinic. To enhance referral, patients are supplied with letters for their family physician and, when necessary, for their specialist, explaining the purpose of the identification program and requesting referral of the patient to a Lipid Clinic. The patient is also supplied with a letter for the clinician at the Lipid Outpatient Clinic describing the results of the DNA analysis and the nature of the FH causing mutation.

Treatment at the Lipid Clinic
Presently, a network composed of Lipid Clinics at 70 university and district hospitals throughout the Netherlands, exists. Here, primary and secondary disorders of lipoprotein metabolism are diagnosed and treated according to uniform criteria. After referral of a FH patient, identified in the program by DNA-analysis, the patient's complete risk-profile is accurately assessed: family history, medical history, lipoprotein parameters, complete blood chemistry including homocysteine, blood pressure and life style (smoking habits, alcohol consumption, exercise, diet). Based on the findings from this extensive examination, medical management is initiated, with the aim to eliminate or reduce risk factors. In the majority of cases, lipid lowering therapy is prescribed and dietary advice is given. Usually the patient is seen for an additional one or two follow up visits and when medical management is satisfactory, the patient is referred back to the general practitioner. Criteria used for diagnosis and treatment are assessed during biannual meetings of the participants of the Lipid Clinic Network.

FH Registry

Participants of the Lipid Clinic Network are equipped with a similar computerised data base in order to record the data obtained from the medical examination in an uniform fashion and to keep track of changes in the patient's health condition, also with regard to tolerance of and response to lipid lowering therapy. When centralised, these clinical data, recorded by Lipid Clinic Network participants, constitute the national FH Registry. Analysis of data in the FH Registry not only will yield valuable information on the effects of early diagnosis and long term treatment with respect to health benefits and cost-effectiveness, but above all, may resolve issues dealing with the variable clinical expression of FH. By investigation of a large cohort of clinically well-documented patients, classified in homogeneous groups according to type of FH-causing mutation, a better understanding of the disorder FH with regard to time of onset and the severity of symptoms and the manifestations of atherosclerosis, response to therapy and interaction of various risk factors, may be obtained.

Results obtained

To date, a clinical diagnosis of FH was confirmed by the demonstration of the presence of one of the 110 LDL-receptor gene mutations known to be present in the Netherlands in over 2500 patients (index-cases). Starting from a small number of index-cases, over 4000 persons were enrolled in the identification program. In this group, more than 1500 individuals were diagnosed as having FH, as determined by analysis of their LDL-receptor gene and the presence of a LDL-receptor gene mutation. This implies that 3 to 4 family members have to be examined by DNA diagnostic procedures to identify one obligate FH patient. It is evident that the approach of selective family screening is far more efficient than screening the general population for elevated blood cholesterol levels. Results of the identification program and the characteristics of the patients identified are listed in Table 9.

Table 9: Results of the national identification program in the period of January 1994 until December 1998

number of index cases	225
number of family members analysed	5431
carrier of a mutation	36%
carriers over 18 years	69%
carriers under 18 years	31%
hypercholesterolemia (TC>7.5 mmol/l) known prior to identification	45%
on drug therapy prior to identification	34%
not on drug therapy prior to identification	66%
on diet therapy prior to identification	2.8%
patients with evident CVD	7%
referral and treatment after identification	93%

Participation by persons in the program was excellent. Only on rare occasions has participation been refused for unexplained reasons. Our experience from family studies entails that there is a high degree of anxiety in most families, caused by the fact that a number of family members either passed away suddenly or suffered from a myocardial infarction at young age. By investigating these families, the majority (66 to 75%) of family members could be reassured, since they were not carriers of the FH-causing mutation. They could be informed that their risk for premature cardiovascular disease was not severely elevated and that they could not pass the disorder on to their children. For those who were found to be carrier, in many cases a certain amount of relief was brought, since their, until then unexplained, high cholesterol level was now understood and could be managed effectively.

The discrepancy between the number of persons who knew that their cholesterol level was elevated, and the actual number of persons treated for this condition, was remarkable. Apparently elevated cholesterol levels, also those in the pathological range, are still considered by many general practitioners to be the result of poor life style or dietary habits, but are not adequately managed. Even in a group of 118 patients with known cholesterol levels of 12 mmol/l or higher, more than one-third was not offered treatment.

The high proportion of patients under 18 years of age, identified by the program, suggests that there is ample opportunity for primary prevention, while, on the other hand, an impressive proportion is still available for secondary prevention. After identification, the majority of patients was convinced of the seriousness of their condition since more than 90% of them reported to a Lipid Clinic for further assessment and treatment.

Extension of the model

Once an infrastructure has been established, the model could be extended to other dominant genetic disorders, although not all conditions laid out by the WHO, may be met. In this respect, the availability of an effective treatment is the most important criteria. One suitable candidate could be Familial Combined Hyperlipidemia (FCH). FCH is associated with an increased risk for premature atherosclerosis, to a similar extent as FH, and is a frequent disorder. Recognition in an early stage and adequate treatment would certainly result in a better prevention of atherosclerotic complications caused by FCH. A drawback is that unequivocal diagnosis is not yet possible, since the molecular basis of FCH has not been elucidated. In this particular case, diagnosis would rely on clinical criteria only, posing special complications to the laboratory and genetic field work components of the model.

In the field of vascular medicine, other disorders which can be approached in a similar fashion include hyperhomocysteinemia, inherited malignant hypertension or long-QT syndrome.
In regard to other dominant genetic disorders with late onset, the availability of an efficacious therapy and the impact on quality of life, determines the desirability of a program aimed at the identification of presymptomatic carriers.

For Marfan syndrome (MFS), a disorder of connective tissue caused by mutations in the fibrillin-1 gene, straightforward PCR-based DNA- analysis is available [26]. MFS is associated with mitral valve collapse and dilatation of the aortic root, both correctable by surgical intervention. When undiagnosed and untreated, MFS poses a serious risk for cardiovascular death. A survey among patients with MFS demonstrated that 78% of patients would make use of prenatal diagnosis, when available [27].

This suggests that even for a serious disorder as MFS, of which the risk for cardiovascular complications can be reduced, albeit in a complicated fashion, a program to identify presymptomatic carriers could be justifiable.

Financial considerations

The ultimate aim of the proposed identification program is to prevent morbidity and mortality due to cardiovascular disease. The efficacy of the program eventually has to be expressed in terms of reduced morbidity by, for instance, myocardial infarction. Since long term follow-up is required for the results to reach statistical significance, effects could be estimated by means of intermediate parameters such as lipoprotein levels. Data required to make such an estimate can be supplied by the

national FH Registry. For FH it has been already demonstrated that medication for primary prevention of coronary heart disease is effective and achieves favourable cost-effectiveness [13]. In this case it would be appropriate for governmental institutions to bear the initial costs of a screening program, since early identification of large numbers of presymptomatic carriers and subsequent treatment is expected eventually to substantially reduce the burden on the nation's health care costs.

Ethical considerations

A preventive screening program can not be expected to be beneficial in all respects. Large-scale screening of "healthy" persons may also generate problems. Misunderstanding of test results, stigmatisation and effects on psychological well-being may be a repercussion. Results of such a program may also negatively influence employment or health insurance. Consideration of these potential dangers implies that a screening program can be initiated, only after certain safeguards have been secured. Education of the public, physicians and other parties involved, such as insurance companies, is the most crucial issue. Correct evaluation of the test results by all parties involved, is likely to minimise the adverse consequences and negative complications for the person tested.

Informed consent and participation on a voluntary basis can not be stressed enough. Furthermore, procedures to protect the right to privacy of patients and their family members should be established beforehand.

Final Remark

The basic requirements for a large-scale screening program for FH, i.e. a reliable diagnostic procedure, a genetic field working organisation and centres for referral and treatment, have been established in the Netherlands. The program has been successful in the selective identification and referral of a large group of unrecognised and untreated patients with FH. To warrant follow-up and counselling, registration of patients is indispensable. Furthermore, identification and registration of patients must be accompanied by continuous evaluation with regard to safeguarding privacy, epidemiological and social aspect and effects on cardiovascular morbidity and mortality. Formation of a foundation that represents all parties involved, and has a set of legally approved rules and regulations, can guarantee protection of the privacy of the identified and registered individuals.

7. Conclusions and Recommendations.

Inherited lipid disorders, especially Familial Hypercholesterolemia, are serious genetic disorders, which, when untreated, lead to premature heart disease, disability and death. Principal physicians and investigators have indicated that a variable but high percentage of the total population, up to 7%, can suffer from these inherited lipid disorders. Regretfully, only a small minority of these patients has currently either been diagnosed or appropriately treated.

In contrast, with regard to Familial Hypercholesterolemia, the elucidation of the molecular basis of this disease has made diagnosis at the DNA level feasible in the vast majority of cases. Moreover, treatment of hypercholesterolemia has unequivocally been demonstrated to result in significant reductions in both cardiovascular and total mortality.

Large scale family screening and genetic testing has shown to be highly effective in identifying currently untreated patients. The extend of identification of these patients and the subsequent measures to prevent the consequences of inherited lipid disorders, are grossly inadequate.

All the above demonstrate that inherited lipid disorders pose a serious but avoidable health hazard, which necessitate as well as justify, national efforts to provide both diagnosis and treatment to persons affected with these disorders.

Access to and reimbursement of healthcare provisions and measures are not equally available to individuals and/or countries.

- As inherited lipid disorders are diagnosable and treatable in the primary health care context, treatment should be available on a fair basis of risk when compared to other chronic disorders.

- Governments and national institutes of health should be made aware of the existence of this health hazard.

- Awareness among the general public and the medical community should be promoted. The support of education about these disorders at the public, school, paramedical and medical level is required.

- WHO should issue guidelines for identification, diagnosis and medical management of inherited lipid disorders.

- Specific education about these disorders should be provided at all levels, especially in medical training. There should be skills in primary health care to counsel about the risk of the disease, the dietary modifications and knowledge about statins so that on-going care can be given.

- A focus should be made on the family and the impact that bereavement could have on children. The plight of children with homozygous FH may need special consideration within budgetary

- Constraints for treating risk. If plasmapheresis is not available, statins with proven efficacy in homozygous FH should be considered

- Patients must have unrestricted access to treatment and to cholesterol-lowering medication at no or low costs.

- Long-term follow-up and drug compliance should be assured.

- Research into the genetic and environmental factors influencing the expression of inherited lipid disorders, the development of atherosclerosis and the pharmacology and efficacy of lipid-lowering drugs should be stimulated. An indication is needed for on-going research into the factors influencing heart disease, and how to intervene in the pathogenesis of the atherosclerotic process.

- Specific attention may need to be given to the management of children of this disorder and here careful research is called for the establishment of active patient organisations, focused on the implementation of the above mentioned recommendations, is of utmost importance.

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ANNEX

Progress reports (prepared by members of MED-PED)

Summary of FH activities

Austria (Prof. Kostner and Dr. Schmidt):

When we were confronted in Austria with the goals of MED-PED in the second half of 1994 we first had to solve country specific problems of our health care system. Despite the relatively low number of inhabitants, Austria is divided in 10 counties and part of the health care regulations are under the authorities of each individual county. This is particularly true for health insurance which does not operate federally. As in any other civilised country, most health insurance is heavily subsidised by the government and far from making profit. Thus, any new project which can be foreseen to cost additional money on a short term is, treated with some reservation. When we first stepped into MED-PED, statins were not allowed to be freely prescribed by specialists and only in exceptional cases were they paid by insurance companies.

Austria has no central hospital or clinic which might be responsible to take care of special cases on a country wide basis. Austria has 3 medical schools: in Vienna, Graz and Innsbruck. In addition, there exist numerous larger or smaller county- or community hospitals which operate independently. Given this situation, it would have been impossible to install only one or even two MED-PED centres in Austria to diagnose and treat all FH patients country wide. Our method was to create several "lipid units" (also called "lipid ambulances" or "lipid clinics") in analogy to the "Dutch Model" with particular emphasis on primary and secondary hyperlipoproteinemias. Many of these lipid units emerged from metabolic wards, departments of endocrinology or diabetes stations. In most cases these lipid units were not on duty the whole week but rather 1-2 days or even just several hours per week.

Site of DNA Analysis
At the beginning, we focused on units which had a higher reputation in research or patient care of hyperlipoproteinemias. Given the complexity of the DNA-analysis for LDL-receptor defects, we decided to choose one of these units to install appropriate facilities to run all necessary techniques for characterising genetic defects and mutations. After some debate, it was decided that all DNA analysis would be done in Graz at the Medical Biochemistry Institute (MBC) headed by prof. Dr .G.M. Kostner.

Strategies for FH-Screening
From work published mainly by Helen Hobbs from the Brown and Goldstein group in Dallas, we understood that the most frequent mutations in FH are situated in exon 4 followed by exons 14, 8 and 9 of the LDL-R gene. There was however one difficulty which we feared from the beginning: Austria has and has had a very heterogeneous population with a great ethnic and genetic diversity. This goes back beyond the Austrian Hungarian Monarchy which covered present day Austria, Hungary, Czechoslovakia, Yugoslavia, parts of northern Italy and many more that were unified, merged and co-married together. We expected not a single or only a few "founders" as known for example in South Africa, but rather that multiple founders contributed to the genetic background of our population. We could foresee, that an approach concentrating on only a few specific mutations of the LDL-R gene and spread from there into families, as demonstrated with excellent success in Holland or Southern Germany, would probably yield a very incomplete picture. Thus it was decided to amplify one exon after the other by PCR, followed by DGGE and sequence analysis.

Specific DNA Techniques
In 1994, as we started the MED-PED project, the strategy for genetic analysis was as follows:

1. Exclusion of the apolipoprotein B-100 defect by digestion of specific PCR product with MspI and gel electrophoresis.
2. Screening the exons and their flanking regions of the LDL-receptor gene for point mutations using the DGGE method.
3. Sequencing of those fragments showing aberrant banding patterns on an ABI DNA Sequencer (model 373A) in both directions allowing high identification rates of heterozygotic sites.
4. Detection of large rearrangements by Southern blot analysis.

On average, we perform 41 DGGE analyses to detect one mutation. This number is highly dependent on the exon examined, ranging from 173 for exon 2 to 21 for exon 14. Exons which most frequently carry mutations in Austria are exon 4, 14, 13, 9,10 and 8, yet there were mutations found in most of the

other exons as well. This tells us that screening for few specific mutations is not a strategy which would allow us to characterise the majority of FH index cases on a DNA level. We therefore aim at preferential screening of exons by an accelerated DGGE method as introduced by other groups in Europe as a reasonable approach. Screening for larger rearrangements in the LDL-receptor gene is currently not practised in our lab due to capacity problems.

Canada-Ontario (Dr. Hegele):

(A pilot program to prevent vascular disease and diabetes in aboriginal Canadian communities: the Ojibway, Cree and Inuit)

The Oji-Cree from Northern Ontario have a very high prevalence of cardiovascular disease and diabetes mellitus, whereas the Inuit from Nunavut have a very low prevalence of these diseases. After screening more than 3000 native Canadians, we have yet to identify a single subject with clinical or biochemical features of FH. We are therefore pursuing other candidate genes to try to explain the excess disease burden in the Oji-Cree. We have so far found that there are significant differences between Oji-Cree, Inuit and white subjects with respect to the frequencies of putative "deleterious alleles" of several candidate genes in atherosclerosis and diabetes. Specifically, compared to whites, both Oji-Cree and Inuit have an excess of "deleterious alleles" from 12 candidate genes in atherosclerosis and/or diabetes. However, it would appear that these differences in genetic architecture are not sufficient to account for the wide disparity in disease prevalence between the two aboriginal groups. It is very likely that environmental factors, such as a traditional diet and an increased level of activity, can override an apparent background of susceptibility to these diseases. Full understanding of the genetic component will require more effort because of confounding factors such as small genetic effects, non-mendelian inheritance, gene-gene interactions and gene-environment interactions. However, even before there is a full understanding of the identity of all the genes, and how their products might contribute to disease in an individual or a community, there would be some justification to recommend an intervention strategy at this point in time. Such an intervention strategy would stress a return to a more traditional diet and lifestyle in order to avert and reverse such disease phenotypes in Canadian aboriginal communities.

Canada-Quebec (Dr. Gaudet):

(Familial Intervention Network for the Prevention of Genetic Diseases in the Saguenay-Lac-Saint-Jean (SLSJ) Region)
General objective and pertinence.
In Quebec, there are five Lipid Clinics collaborating with the MED-PED program and with the Canadian Association for Familial Hypercholesterolemia (ACHF). However, the SLSJ region, which is characterised by a high prevalence of FH, is also the only region in Canada where a program on Community Genetics has been officially recognised by health authorities. It constitutes the first officially recognised intervention program in North-America. This program involves the Corporation for Research and Action on Hereditary Disease (CORAMH), a lay-organisation devoted to the dissemination of information and education on genetic determinants, including FH. Its aim is to introduce a familial network for the prevention of genetic diseases in the SLSJ region. This project relates to two priorities of the Federal Funds pertaining to health care service adjustment: primary care reform and integrated health benefit services. It also applies to two objectives of the Quebec health and welfare policy: to reduce the incidence of congenital or genetic defect and lower cardiovascular mortality by 30% by the year 2000. Development of this program will reinforce the actions on FH in a vital like environment: the family.

In addition, this familial intervention network will promote familial diffusion of programs focused on other health problems, such as prevention of cardiovascular disease and anti-smoking programs. Beyond monogenetic traits, several research projects on complex genetic traits are currently in progress in the SLSJ region.

These projects aim at the identification of susceptibility genes involved in disorders such as coronary artery disease.
Information derived from these projects should be used advisedly in affected families. The problem of data utilisation pertaining to susceptibility genes is also at the centre of this projects preoccupation.

Specific objectives:
This project has five specific objectives: 1) to develop familial intervention for the prevention and treatment, when available, of FH and other hereditary diseases in SLSJ; 2) to introduce a familial

intervention network in all sectors of the region; 3) to appraise the effectiveness and impact of the approach; 4) to establish collaboration between the preventive genetics familial intervention network, the cardiovascular disease prevention network and the diabetes education network, in order to reduce the incidence of coronary artery disease and diabetes associated with familial dyslipidemias; 5) to ensure the concepts exportability.

Czech Republic (Dr. Freiberger):

Situation: Approximately 20600 people suffer from FH in the Czech Republic.

Legislative support, guidelines: There is no specific activity on any level focused on FH in our country. However, the Czech Atherosclerosis Society has published the guidelines for diagnosis and treatment of adult patients and children with hyperlipidemias and the Group for Hyperlipidemias of the Czech Paediatric Society has issued similar guidelines for follow-up of children with hyperlipidemias. A selective screening of children with a familial history of premature cardiovascular disease at 5 to 13 years of age is legislatively supported. It has been recommended to test the cholesterol level in every patient older than 30 years who visits a physician for any reason.

Diagnosis and treatment of FH: The patients with FH are diagnosed, followed up and treated by lipidologists in lipid centres and by cardiologists, internists and paediatricians. Their efforts are not co-ordinated and a central registry of patients with FH does not exist. Currently in the Czech Republic one centre performs DNA-analysis of LDL-receptor gene mutations, while a second performs linkage analysis with DNA markers linked to LDL receptor locus. Collaboration among specialists interested in lipid disorders is lacking.

Financial support: Clinical management of patients with lipid disorders includes blood testing and invasive diagnostic and therapeutic procedures in patients with CHD, which is fully covered by the national health insurance system. Costs for lipid-lowering medication are covered from 75 to 100%. DNA diagnostics is not supported at all. There is no special support for activities with regard to identifying new FH index cases or affected relatives of known FH patients.

Education: Specific education of the public with regard FH is insufficient, but education of physicians improves. Conferences and seminars focused on lipid disorders and atherosclerosis are organised, mainly by the Czech Atherosclerosis Society, the Group for Hyperlipidemias of the Czech Paediatric Society and the Institute of Postgraduate Education of Physicians, all with support from pharmaceutical companies. Information on lipid disorders provided by media are sporadic.

FH registries: A national registry of FH cases does not exist. A MED-PED FH registry was started in 1997 in the Research Institute of Child Health in Brno, where the Czech MED-PED group was established. There are 263 patients with FH/FDB (67 of them are children) included in this registry. The diagnosis on a DNA level has been accomplished in 80 patients.

Research projects: A project focused on a direct mutation analysis of the LDL-receptor gene was completed successfully. Another project addressing the frequency of the FDB mutation R3500Q in

the Czech population by analysis of new born blood spots, is on-going and the affected relatives in these FDB pedigrees are being identified.

A third project exploring genotype – phenotype interactions was initiated in 1999. All of the above mentioned research projects are supported by the grant agency of the Ministry of Health of Czech

Republic. A proposal addressing LDL-receptor activity testing has been submitted to the Bristol-Myers Squibb company for financial support.

Perspectives: The main goal is to expand the number of FH cases identified and treated and to initiate a national registry of FH cases. The Czech MED-PED group has already started to establish a network of MED-PED collaborators by sending letters and questionnaires to lipid specialists, cardiologists, internists, paediatricians and primary care physicians through the appropriate medical societies.

We are trying to set uniform FH diagnostic criteria in our country.
The diagnosis should be confirmed by direct DNA analysis, which is a very helpful diagnostic tool, especially in identifying the affected relatives of FH index patients. A reliable diagnostic procedure to determine LDL-receptor gene defects is available at the Research Institute of Child Health in Brno. This procedure of systematic and more intensive search for affected relatives is a model that could be applied throughout the whole country. To date, our requests for financial support for a staff member to contact relatives of FH patients has not been granted. The co-operation among specialists interested in lipid disorders needs to be improved. It will be necessary to work with the Ministry of Health for possible support of the MED-PED project. Obtaining financial support for the above activities, especially for education of the public and physicians, for identifying the affected relatives of FH patients and for DNA diagnostics of FH, is our highest priority. Materials published by the WHO and MED-PED, will be useful in developing further activities to find FH cases and especially useful for documenting the need for financial support for this cost-effective method.

Denmark (Prof. Faergeman):

The incidence of Familial Hypercholesterolemia (FH) in Denmark was at least 1 in 1000, based on family studies after measurements of chord blood concentrations of VLDL- and LDL-cholesterol [28]. The true incidence could well be as high as 1 in 500, the usual estimate in most populations. Within the Danish population of approximately 5 million people, up to 10,000 can therefore be expected to have FH. Many of them are probably treated by their general practitioners or local hospitals, but it is likely that most FH patients remain undetected. A national collaborative effort to detect FH patients was therefore established in 1997 between FH researchers of the universities of Aarhus and Odense. The collaboration is a project supported by a 5-year grant from the Danish Health Science Research Council.

The organisation of the project reflects the organisation of the whole Danish health care system. This system is very decentralised. The 14 counties in Denmark, rather than the Danish state, have most of the responsibility for the delivery of health care. The work of both general practitioners and hospital specialists is therefore organised by county rather than country, and detection of genetic diseases such as FH occurs across boundaries. The molecular diagnosis and most initial clinical counselling of patients with FH are performed at Aarhus Amtssygehus University Hospital and at Odense University Hospital. But at least one cardiologist or other clinical specialist in each county has assumed the responsibility for continued counselling of patients detected by family screening and for advising the general practitioners entrusted with the care of these patients.

Molecular diagnostic strategies in Aarhus and Odense are roughly the same: screening of coding regions, flanking sequences and promoter regions of the LDL-receptor gene for mutations by single strand conformational polymorphism (SSCP) analysis or by denaturing gradient gel electrophoresis (DGGE). Genetic variation is then analysed by gene sequencing. If no mutation is found, long PCR or Southern blotting are used to detect large gene rearrangements. A cleavage analysis of the apolipoprotein B gene is done to detect the R3500Q-mutation.

The molecular diagnostic work in Aarhus and Odense is now performed on a semi-routine basis by the departments of Clinical Biochemistry. Clinical work-up, evaluation of degree of cardiovascular disease, initiation of dietary and drug treatment and genetic counselling are done by the departments of Cardiology. In Aarhus, LDL-apheresis is performed in selected patients with homozygous or very severe heterozygous FH [29].

Partial reimbursement (75%) of costs of lipid lowering drugs, including statins, currently requires application on an individual basis to the National Health Board (Sundhedsstyrelsen), and FH is one of the several criteria for granting reimbursement. Danish insurance companies have not formulated policies concerning DNA-testing, but they have developed a common policy for setting insurance premiums as a function of serum cholesterol before and during treatment.

France (Dr Pascale Benlian):

Lipid disorders are generally known among the French public as acquired conditions resulting from inappropriate dietary habits. Due to little public awareness that these disorders underlie cardiovascular disease, health care efforts are mainly focused on curative approaches.

Moreover, in comparison with other cardiovascular risk factors such as diabetes or hypertension, lipid disorders do not benefit from coherent efforts in the health care system. Care is provided for the greatest number, with no specific regard for the patients at higher risk. Thus, there are very few objective data available concerning FH in France.

Large scale screening in primary care for hypercholesterolemia is not organised. Centres for preventive medicine, supported by the social security insurance system, contact individuals from the general population for health check-ups. In the Tours Centre, during the year 1990-1991, among 65 000 males and females over the age of 6 years, 2% had a total cholesterol level of over 7.8 mmol/l (300 mg/dl) and 5% had a level over 7.3 mmol/l (280 mg/dl). In France therefore, 1.16 million persons will have significant hypercholesterolemia, among which the majority of the FH patients can be found. Since 1985 MONICA registries exist in Toulouse, Lille and Strasbourg. A survey among 300 000 men aged 35 to 65 years, demonstrated that 66% of the individuals with a high cholesterol level had their lipid levels tested, that 25% was treated, but that only 16% was treated appropriately. Based on these observations one may assume that 97 000 patients with FH are not identified and treated.

Health care for patients with FH is mainly provided by general practitioners. These physicians however are not trained with regard to patient education, dietary advice, patient follow-up and tracing of relatives. Recently the government implemented general regulations in order to prevent excessive lipid testing. In addition, there is little knowledge among physicians about the value of medical family history and the typical clinical signs and symptoms of FH. The clinical characteristics of FH are often confused with those of FCH. The predictive value of LDL-cholesterol testing and the treatment targets when correcting hypercholesterolemia in not generally accepted. Primary education is provided by academic hospitals and continuing education of physicians about lipid disorders is mainly provided by pharmaceutical companies by means of scientific meetings, brochures etc. Again, no specific information on FH is available. Education of the public mainly relies on the media, but very limited time is allotted for lipid disorders and none for FH. There are however, specialised lipid clinics in the academic hospitals of Lille, Lyon, Nantes, Nice, Toulouse and Paris. They collaborate with clinical laboratories, imaging units and dieticians. The clinic in Paris acts as a centre for establishing the genetic diagnosis in FH patients and their relatives. Active tracing of relatives by genetic field work is not available. In general there is a lack of co-ordinated efforts to diagnose, treat and trace families with FH.

The government has issued general guidelines which in principle support the diagnosis and treatment of lipid disorders. Under certain conditions blood testing, medical consultation and medication is reimbursed. However, priority is given to curative treatment of cardiovascular disease, which is still the leading cause of death in France. Consequently there is no support for large scale measurements of LDL-cholesterol levels or genetic testing for FH, nor for patient and physician education, long-term treatment and follow-up. Awareness of the necessity of networking is growing, although aimed actions have not been undertaken yet.

In 1994 a MED-PED FH registry was established in Paris, starting with patients referred to the local lipid clinic. The register is in development. Genetic testing for LDL-receptor gene mutations was started only in 1998. In parallel efforts were developed to use direct LDL-cholesterol measurements in order to discriminate FH from FCH. The Medical Faculty in Paris, supported by the hospital, provides continuing education to physicians.

China, Hong Kong A.R. (Dr.Tomlinson):

There have been few descriptions of FH in Chinese subjects in the literature and the frequency is not known. The prevalence of hypercholesterolemia (total cholesterol over 6.2 mmol/l) was 12% in men and 13% in women in a recent population survey in Hong Kong [30]. Data from Taiwan, showed that hypercholesterolemia increased with age but was generally only half as common as in the USA or Europe [31]. In rural parts of mainland China, cholesterol levels have been lower but in a study in urban Shanghai started in the 1970s where the mean serum cholesterol in the cohort was 4.2 mmol/l, it was shown that CHD mortality was still related to blood cholesterol even at these lower levels [32]. It has been reported that subjects with heterozygous FH in parts of China may go unrecognised because their cholesterol levels are not markedly raised and they have few clinical stigmata of tendon xanthomata or premature CHD [33]. This was probably the result of the very low fat diet taken by that population rather than the mutations involved in causing less impairment of LDL-receptor function. Another report from China suggested that clinical experience indicated that heterozygous FH was a common disorder leading to atherosclerosis and CHD [34].

The situation is probably changing with the rapid economic development in Asian countries [35].

Our experience in Hong Kong, is that Chinese patients with FH manifest in a similar way to those in western countries and Japan, although the risk of CHD appears less. We have conducted a study, partially funded by the Hong Kong Research Grants Council, to examine the clinical manifestations and to identify the underlying genetic mutations in the LDL-receptor gene. Probands and their affected family members were clinically identified as having definite familial hypercholesterolemia if: (a) fasting plasma total cholesterol > 7.5 mmol/L (>6.5 mmol/L in individuals younger than 16 years) and having normal fasting plasma triglyceride levels, and (b) presence of tendon xanthomata in the proband or a first degree relative, or a pattern of hypercholesterolemia in their family of dominant inheritance. 143 patients from 53 families were clinically classified as definite FH. These subjects were aged 38±16 yrs (mean±standard deviation; range 5-84 yrs). The average plasma lipid levels (mean±SD) of these patients were total cholesterol 9.4±1.5 (range 6.0 - 13.3), LDL-cholesterol 7.5±1.5 (range 3.3 - 11.7), HDL-cholesterol 1.34±0.4, triglycerides 1.4±0.9 mmol/L (range 0.3 – 5.0). A total of 30 unrelated patients were recruited for investigation of the mutation in the LDL receptor gene. There was 18 different mutations detected in 21 of the probands, 11 of which had not previously been described [36]. 69 first-degree relatives of these 21 subjects with mutations were also available for genetic testing and 45 were found to have the same mutation as the proband of their family [37]. Some mutations were found in more than one family and may turn out to be common mutations in Chinese populations [38] as is the case in Japan where five mutations account for over 30% of the cases [39]. In some families with clinical FH, no mutation in the LDL-receptor gene could be found so other genes may be involved. The common mutation in apolipoprotein B, R3500Q, causing familial defective apolipoprotein B-100 was not detected in Chinese patients in Hong Kong.

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Hungary (Dr. Czeisel):

MED-PED FH program: To date, 10 centres have been established and 176 index cases and 266 first degree relatives with FH have been detected. Thus, the total number of registered FH cases is 442.
In Hungary, the so-called euphenic model for the prevention of early onset coronary artery diseases, particularly FH: a network of peri-conceptional care was established in 1989 and includes 30 centres. The main objective is to use the available methods of family planning in one program, in addition to conducting feasibility studies of some new programs. One of the latter was the euphenic model to check the feasibility of the MED-PED program among population-based youngsters (mainly twenties). The genetic predisposition was revealed on the basis of case and family history as well as by cholesterol screening in both prospective mothers and fathers. FH was identified in 7 of 3530 women and in 10 of 3127 men in the first part of the study. Thus one heterozygous FH patient was found in 504 women and in 313 men.

Media and educational activity: In 1995 a series of TV programs, including eight presentations and discussions, were organised to popularise the MED-PED FH program. In 1997 a special program for pharmacists was organised (review, special section of national congress, posters in all drugstores)

Scientific activities: have been conducted with familial defective apolipoprotein B-100 (FDB) in 1997. Four patients with FDB (R3500Q-mutation) were diagnosed with allele-specific PCR and the mutation was detectable also in 9 cases out of 11 living family members.

Others: In Hungary the fortification of bread with folic acid, vitamin B6 and B12 was introduced in 1998 to reduce the occurrence of hyperhomocysteinemia-related vascular diseases and congenital abnormalities, particularly neural-tube defects.

Iceland (Dr.Gudnason):

Iceland aims to identify all FH patients by the end of the year 2000. Limited population size, easily accessible genealogical information and willingness by family members to participate in a screening program, makes Iceland an ideal country for systematic identification of carriers of mutations in the LDL-receptor gene, which cause FH. Thus preventive medicine can be applied in a more effective way. One mutation has been found to account for 60% of FH cases in Iceland.

A feasibility study demonstrated that all families with this mutation can be traced back to a common ancestor in half of the cases, going back not further than the 18th century. By tracing the families back for as many generations as possible and identifying the first relative alive when tracing forward again, key individuals representing an nuclear family were identified. Of those tested, 15% were a carrier of the mutation, meaning that 1 in every 6 tested has FH. This is a 80-fold enrichment compared with the 1 in 500 in the general population. These results are extremely encouraging. Negotiations are presently taking place with the Data Protection Commission and the Scientific Ethics Committee of the Ministry of Health in order to obtain permission to systematically test for FH in Iceland and reach our goal of identification of all FH patients by the end of the year 2000. Support from the International MED-PED FH program and the WHO is required to convince the Icelandic authorities.

The Netherlands (Dr. Defesche):

(MED-PED in the Netherlands: a practical approach of FH case-finding)

In the Netherlands the three basic requirements for identification of persons with FH have been established:

In a central DNA-diagnostics laboratory, an accurate and reliable diagnostic procedure to determine LDL-receptor gene defects, the underlying cause of FH, is available. For the 110 characterised LDL-receptor gene mutations, known to be present in the Netherlands, detection assays based on the polymerase chain reaction (PCR) technique, have been developed.

An organisation for identification and localisation of index-patients and their family members throughout the country has been set up. By employing a number of genetic field workers, this organisation implements FH case-finding and acts as an intermediate between the DNA-diagnostic laboratory, the identified patients and the centres for referral.

Presently, a network of Lipid Clinics at 70 university and district hospitals throughout the Netherlands exists. Here, primary and secondary disorders of lipoprotein metabolism are diagnosed and treated according to uniform criteria. Lipid Clinics submit blood samples of clinically diagnosed FH patients to the DNA-diagnostics laboratory for DNA analysis.

Molecularly characterised FH patients act as index-cases from which nation-wide family investigation is initiated. FH patients, identified in the program by DNA-analysis, are referred to one of the Lipid Clinics, where the patient's complete risk-profile is accurately assessed.

Costs generated by routine DNA-diagnostics and the genetic field work are covered by special grants form the Ministry of Public Health, while costs generated by Lipid Clinics and DNA-analysis to identify index-cases, are reimbursed by regular health insurance. Co-operation in the program is high: over 95% of persons contacted was willing to participate. The costs for the participants are limited or nil, which is an important reason for the high rate of participation. In January 1997 a 3-year evaluation study was initiated by the Institute for Social Medicine of the University of Amsterdam. This study will address the validation of DNA-analysis versus cholesterol measurement, psychological and social effects of the identification program and its cost-effectiveness. Preliminary results of a survey among almost 650 participants are very favourable and await publication.

After its initiation in 1994, the program has identified over 2000 FH patients by examining approx. 5400 individuals. Together which the patients identified by the Dutch Lipid Clinic Network, the total number of FH and FDB patients identified and registered in the Netherlands amounts exceeds 7500 (March, 1999).

In the Netherlands the StOEH, originally initiated by the Amsterdam Lipid Research Group and now an independent government-supported FH case-finding organisation, is very active identifying ALL patients with FH within a reasonable amount of time (less than 10 years). Case-finding is performed by genetic testing of first and second degree family members of FH index-cases. For this purpose we presently employ 5 genetic field workers, who travel the entire country, visiting family members for blood sampling. Of all individuals tested, 40% is a FH patient by DNA diagnosis.

The Amsterdam Lipid Research Group co-ordinates the Dutch Lipid Clinic Network, in which approx. 70 hospitals participate. Members of the Lipid Clinic Network are committed to FH case-finding and many sent blood samples of clinically diagnosed FH patients for DNA-analysis.

Confirmation of the diagnosis by DNA-analysis generates the index-patients, on which the national FH case-finding is based. We maintain the largest Lipid Clinic for adults and children in the Netherlands, with thousands of patient contacts per year. Most FH index-cases are derived from our Lipid Clinic. Our group is continuously involved in clinical trials and patient related clinical research. We have initiated several research projects and co-operate with many national and international groups on related subjects. Our major areas of research include the molecular basis of FH, improvement of DNA-diagnostics (high-throughput DNA-analysis), gene-gene and gene-environment interactions.

New Zealand (Dr. Mann):

MED-PED is active in both the Otago and Canterbury regions of New Zealand, and once fully established here will be extended further. Otago data only is available here. We are now liasing with Medical Centres and General Practitioners to recruit patients with Familial Hyperchole-sterolaemia. We have had some success also with Public meetings and articles in the local newspaper. A very enthusiastic support group is underway and brochures and posters are ready for distribution. Problems initially in getting the project up and running, occurred because an outdated version of the MED-PED computer program for data collection. We hope to have an updated version from MED-PED Australia by late May/June. Meanwhile lists and family trees are still being collated on basic Microsoft Word and genealogy programs. We have extensive data on approximately 35-40 families and are making good progress with a different 35 families. Our priorities are to re-establish contact with families from previous studies, (20-30 years ago), and contact their now extended families. This phase is currently being implemented.

We have collaborated recently with Professor Steve Humphries (UK) on genetic aspects of plasma lipid lowering diets and expect to continue this association during the current project.
Despite lack of resources and funding, we are extremely enthusiastic to have this project fully established in as short a time as possible.

Norway (Dr. Ose):

Familial Hypercholesterolemia seems well recognised in Norway although the severity and need for early diagnosis and treatment are not yet accepted. Much focus has been on the attitude towards genetic screening of FH. According to privacy laws in Norway, physicians are not allowed to directly contact persons with genetic disorders who are not their patients. We studied attitudes of this type of screening from a representative sample of the Norwegian population and a group of patients with FH. The majority of both groups were positive about detecting individuals with FH by physicians contacting relatives directly. The majority of both groups also answered that they wanted to know if they could be affected based on the diagnosis of their relatives. Both groups wanted this information regardless of their risk of being affected. We concluded that privacy laws should be changed to meet the attitudes of the population and the patients so that physicians may contact relatives directly.

In 1998 the government was asked by the majority of the Parliament to make changes in the laws allowing physicians to contact relatives directly if necessary. This was the result of more than two years of focus in the media and in the Parliament/Government on genetic screening.

Our estimate of FH in Norway is 15 000 patients with less than 25% being diagnosed. Our FH registry has about 500 index patients and 1.74 FH relatives are registered for each index case with FH. We have concluded that a majority of the FH patients are not yet diagnosed and not yet treated.
A close collaboration exists between the Lipid Clinic at the Rikshospitalet and the new Medical Genetics Laboratory established at the Rikshospitalet in June 1998. The laboratory is headed by Dr. Trond Leren who has moved from Ullevål University Hospital and brought with him his research group. The laboratory is integrated in the Lipid Clinic and both are part of the Medical Department. The Lipid Clinic and the Medical Genetics Laboratory are acting as one centre and will provide therapeutic and diagnostic service for the entire country. Whereas treatment of FH patients in principle will be performed by local GPs, internists and paediatricians, it is the ambition of the Medical Genetics Laboratory to act as a national laboratory. The MED -PED organisation that we are trying to establish in Norway will hopefully have many similarities with what has been successfully established in the Netherlands.

The Government has so far shown no interest in supporting this work that started at the Lipid Clinic in 1989 for FH patients. The Lipid Clinic is working more or less as an unofficial national centre for FH without receiving any support from the Government.

Poland (Dr. Drewla):

The Polish population consists of 38.6 million inhabitants and is generally homogenous.
Although the public has become more and more aware of lipid disorders over last years, hyperlipidemias still are thought to be mostly acquired conditions resulting from unhealthy life-style habits. Special care is provided to those hyperlipidemic patients at higher risk in secondary prevention but many people at high risk of developing premature coronary heart disease are left uncontrolled despite their high cholesterol levels. This situation creates a great task for wider control of hyperlipidemic patients, including familial hypercholesterolemia. Thus efforts are underway to find and treat FH patients.

This search for FH patients in Poland has gained an organised form since we have joined MED-PED in October 1997 – as a result of the WHO meeting in Paris. Although we have been interested in FH for a few years, it was last October that our work began to accelerate. Since 1994 we have been working on development of a system of primary and secondary prevention of CHD in the Northern region of Poland.

Gdansk is the first and so far, the only Polish centre participating in MED-PED movement but there are other centres in Poland dealing with FH. All of them diagnose FH on the basis of clinical criteria. As far as we are aware there is no official FH registry covering the whole country yet.

Unfortunately we have not yet achieved the element that seems to be very basic in diagnosis of FH. We are unable perform the genetic analysis of LDL-receptor gene mutations and therefore cannot confirm the diagnosis of FH accurately. We co-operate closely with the Genetics Department of our University and work quite successfully on some gene polymorphism including ACE, ANF, AT1 and receptor genes studies, which were published in Polish journals and presented
at international meetings. One of our colleges, Karolina Ochman is working on introducing basic genetic analysis of LDL-receptor gene mutations (including SSCP) and we hope to start the method soon. Since genetic testing is very costly it is very hard to find adequate means to work out a molecular technology.

Despite this situation, we keep pursuing the necessary funds in order to start the molecular analysis. We have just received a promising offer from the German MED-PED team for training of our staff in German laboratories and co-operating on genetic and technical matters. In the meantime we collect blood samples of FH-suspected patients, isolate the DNA and store it for future analyses.
Since we are unable to make a genetic diagnosis of FH, we employ both the validated clinical criteria presented by MED-PED members and the "point scoring" criteria proposed by the Dutch team. We find them very helpful in diagnosing FH, but we have to admit that few physicians know them as they often miss obvious cases that completely meet the criteria. So far we have found 42 persons with the clinical diagnosis of FH according to either the Utah or Dutch team criteria. We tend to use contacts of members of the families, but we conduct case-finding ourselves as well. We currently find about two FH patients per pedigree. Although we have found many possible index cases, we often find it impossible to confirm the diagnosis. Access to pediatric patients with FH is limited and xanthomas are rarely seen (one case found). We still have little opportunity to explore families actively and mostly rely on the co-operation of the affected family members.

As a part of our work of finding and diagnosing new cases with hypercholesterolemia, we keep in touch with the rising number of public and private laboratories doing lipid level measurements. They usually give us access to their databases so that we can identify the high-cholesterol patients and get in touch with them to make further examinations. Once a patient contacts us, we provide follow-up to prevent present or future coronary events.

We established a Lipid Clinic in October 1997 that helps us contact and care for hyperlipidemic patients. We provide mostly secondary prevention but also follow high cholesterol patients who have not developed CHD. Thanks to nation-wide educational programs their number raises continuously. There are a few other lipid clinics in our region and many more in the country, but since they work under different administrations the collaboration between all has not been very good. We plan to organise them and unify our approaches to patients for the best research and care. We routinely contact them in order to collect blood samples of hyperlipidemic patients for DNA analysis.

General practitioners in Poland represent different opinions and attitudes towards CHD prevention. Most of them are well aware of the importance of CHD prevention but some do not understand how dangerous high cholesterol levels can be. Unfortunately, very few know the simple FH clinical diagnosis criteria.

Therefore we try to provide education and information to the primary care physicians. Educational meetings are organised and informative materials and brochures for both physicians and patients are distributed.

Unfortunately, general practitioners often do not co-operate in searching for hyperlipidemic patients (they do not find enough time) Because of general financial problems it has been impossible to establish new posts for lipid specialists, nurses and screening workers. Cardiologists are the ones that have the greatest interest in searching for hyperlipidemic patients. The single most important problem at the moment is the very high cost of treatment with statins. Monthly treatment with moderate doses of these drugs is about 10% of an average salary, only half of the price of statins being reimbursed by the state.

Because current activities conducted by various health care units seem to be individual and not very well co-ordinated, we seek ways to unify and incorporate more units into one care system.
Although it requires a large amount of time to complete, we already observed better contact between care units resulting in more effective care. Besides our activities, there is currently a project sponsored by a pharmaceutical company, called "Vita Longa", aimed at professional and integrated care for hyperlipidemic patients. We plan to combine this project with our MED-PED-connected activities.

Another field of development is a computerised information system, which has developed quickly without any external help as the technology gets cheaper and more sophisticated. A co-ordinated network is needed for these databases.

Cholesterol blood testing in secondary school pupils and other specified populations, have ethical questions that currently limits its use.

We continue to encourage both local and central authorities to start educational and cholesterol screening programs in larger populations and to support MED-PED activities. Some beneficial changes are expected after transformation of our health care system.

Few funds are available for educational materials, in co-operation with local private sponsors. We keep in touch with the media and they publish educational articles systematically, that we provide to them. We also encourage the media to enlarge their health and lifestyle sections and we help them to maintain a high professional contend.

The health care system in Poland has undergone a transformation, carried into effect since January 1999, but this transformation does not seem to be well-prepared. More attention towards prevention was expected in the new system, as well as better conditions for diagnostics and treatment of dyslipidemias. Unfortunately, patients with hyperlipidemia have lost part of their reimbursement for the costs of statins, specifically those who are treated as primary prevention. Preventive measures have become more the responsibility of primary care staff, by which patients access to specialist has become even more limited. As our transformed health care system seems to be unfavourable for hyperlipidemic patients, we have established the Society of Patients with Familial Dyslipidemias, that we hope will help those patients to stand up for their rights in this changed situation.

We hope that our efforts to establish an integrated care system for CHD prevention will find an independent position in at least the Northern region of Poland. Our allies among the government officials do their best to establish a priority for CHD prevention and lipid control in the future.

In the year 2000 we will organise a meeting of the Working Group on Prevention and Epidemiology of the European Society of Cardiology in Gdansk which we hope will help us to encourage the officials to pay more attention to our efforts.

Russian Federation (Dr. Schwartz):

(Summary of FH activities in St.Petersburg)

The Russian population consists of about 150 million inhabitants. It is a very heterogeneous population: about 100 nationalities and ethnic groups. Unfortunately, up to now there is no federal program focused on detection, registration and treatment FH patients in Russia. That is why data on frequency of FH in the general Russian population, nor in national or ethnic subpopulations are not available.

In 1995 the FH-Working Group was created in St-Petersburg. The FH-Working Group consists now of the Lipid Clinic of the Institute of Experimental Medicine and three research groups: the Laboratory of Human Molecular Genetics (Head - Prof. Eugene I. Schwartz) of the St.Petersburg Institute of Nuclear Physics; the Department of Molecular Genetics (Head - Prof. Vladimir S. Gaitskhoki) of the Institute for Experimental Medicine and the Department of Biochemistry (Head - Prof. Alexander D. Denisenko) of the Institute for Experimental Medicine. There is also a pediatric service allowing us to care for children with high levels of plasma blood cholesterol early in life.

As a result of the activity of FH-Working Group, 115 unrelated FH patients and 115 available relatives were found in St-Petersburg. The diagnosis of FH has been established on the basis of high LDL-cholesterol levels, a positive family history of myocardial infarction and also often the presence of xanthomas. By DNA-analysis we have found, in addition to several LDL-receptor gene polymorphism, 7 mutations: one large deletion and 6 point mutations or minor deletions. Six of the 7 mutations found were new, not described previously and probably specific for the Russian population: a deletion of 5 kb of exons 3 to 5, C127W, C139G, 347delGCC, C146R and E397X. The only previously reported mutation, detected in the St.Petersburg population, was a deletion of G at position 197 (deltaG197), responsible for one-third (7 out of 22) of unrelated Jewish FH cases in St.Petersburg. By DNA-analysis, the diagnosis of FH could be confirmed in 30 patients. Currently, the intensive search for mutations in undiagnosed FH patients is continuing. We also test genetic loci related to pathogenesis of CAD, including the genes involved in the renin-angiotensin system, the coagulation system, the lipoprotein and homocysteine metabolism, in a cohort of FH patients in order to understand the variability of CAD in these patients.

During the last three years, under difficult economical conditions and extremely limited in research budgets, especially after the financial crisis in August 1998, we have tried to analyse the molecular basis of FH in the St.Petersburg population. To our knowledge, St.Petersburg is the only city in Russia where molecular genetic analysis of FH is being performed. We would like to express our gratitude to Merck, Sharp & Dohme for an annual grant of 10 000 USD. This grant has allowed us to continue our work during the last six months.

We are open for collaboration. It seems reasonable to compare the clinical phenotype of FH patients with the same mutation in different parts of the world, starting, for example, with the deltaG197 LDL-receptor gene mutation. To our opinion, comparative analysis of clinical and biochemical characteristics of patients with the same mutation in different regions, will allow us to draw conclusions about the role of environmental factors in the development of the clinical phenotype of FH.

Russia (Dr. Malyshev):

We have analysed data on a group of about 2,000 patients with hyperlipidemia. In this group, the incidence of FH was 7%, that of FCH 10% and that of severe polygenic 13,5%. The total incidence of inherited lipid disorders in the group studied was 30.5%.

The Cardiology Research Complex has a group of scientists dealing with dyslipoproteinemias. FH is the focus of our research and clinical interest. Currently we concentrate on tracing both index case and affected family members. All data are entered into a computer database. In collaboration with workers at the Molecular Endocrinology Department, we have started DNA- diagnostics, which resulted in the identification of 2 families with FDB caused by the R3500Q-mutation.

In the near future we plan to identify LDL-receptor gene mutations. Preliminary results indicate that original Russian mutations may exist, that are different from those found in European countries. Our experience shows that the majority of persons with FH is not identified and treated in Russia. To date, we have about 150 patients (index cases) with heterozygous FH and 4 clinical FH homozygotes. After persons are diagnosed with FH, they are usually given advise about diet and medication (statins). In some cases they are treated with plasmapheresis. The clinical diagnosis of FH is based on the US MED-PED diagnostic criteria. In 14 patients, we have studied the LDL-receptor activity of fibroblasts, confirming the diagnosis in all cases. We hope that collaboration with the MED-PED community will help us in our work on FH.

South Africa (Dr. Marais):

INTRODUCTION
FH, as well as a few other genetic disorders of lipoprotein metabolism, has only recently been comprehensively described. Since the description of FH and allied disorders has happened in an era of diminishing resources for health care, the practical implementation of these advances is being delayed largely because there is no official recognition of this disorder. Recognition of the disorder is important as it carries a high risk, and treatment of the complications is expensive but avoidable through good patient management involving lifestyle changes and simple and safe drug treatment. The MED-PED collaboration has given itself the task of making the condition known to medical practitioners, health planners and the public.

THE SCALE OF FH IN SOUTH AFRICA
South Africa comprises about 40 million people, distributed somewhat variably in 9 provinces. FH is unevenly distributed across the population. The population consists of several groups, of which the majority is black but there are other recognisable large groups such as white Afrikaans-speaking (Afrikaner) and Coloured (mixed ancestry). Other smaller communities exist.

A high prevalence of FH in the Afrikaner was recognised in the decade ending at 1980 by virtue of the fact that there were many homozygotes for the condition [40]. Research in this community identified a prevalence of about 1 in 75 persons, leading to the recognition of a founder effect to explain the almost 10-fold enrichment of the disorder [41].

Subsequently, FH was identified in several other population groups with postulated founder effects in Jews at an estimated prevalence of about 1 in 100 persons [42]. Several mutations have been described in persons of Indian descent, and a high prevalence is suspected especially in those from Gujerat [43]. The Lebanese immigrants, coming from a country where a founder effect is also known for FH, were also thought to have a high prevalence of FH in South Africa but constitute a small community.

Although lipid metabolic errors were thought to be rare in blacks, their existence was recognised in the decade after the documentation of the high prevalence in Afrikaners [44]. The suspicion is that this large sector of the population has the same background FH prevalence as most other populations. Patients of mixed ancestry, although constituting the bulk of the diagnosed and FH subjects at the state health clinics in some of the provinces, are likely to have a similar prevalence of FH to most other populations. Using the prevalences given above, the FH burden in South Africa can be calculated to be about 120 000. Owing to the high prevalence of the gene for FH in the Afrikaner, almost half of the FH burden falls in this community.

Much of the FH in South Africa has been characterised at the molecular level and many more mutations have been characterised after the review of monogenic hypercholesterolemia [45]. Although the phenotype of FH lends itself to clinical diagnosis, not all cases can be diagnosed with certainty at a clinical level. Genetic diagnosis can be made reasonably frequently in our context because of founder effects in certain communities.

The experience from Britain indicated that the average age of death for males with FH is 43 years [46]. Clinical experience from our 2 clinics actively involved in the MED-PED collaboration, indicates that the same applies to all our FH patients, including the few cases of blacks referred to our coronary care units and lipid clinics. Accepting the prevalences as given above, the country has a large burden of about 200 homozygous FH subjects who mostly die of coronary artery disease before the age of 30 years if not treated with plasmapheresis. There appears to be little familial binding defective apolipoprotein B100 in South Africa. A potential large scale problem for atherosclerosis particularly in our black population, was recently identified is an autosomal dominant type III Hyperlipidemia owing to a mutation in apolipoprotein E [47].

FH IN THE SOUTH AFRICAN CONTEXT
South Africa is a country which has a well-recognised blend of the diseases of developed and developing countries. The country has a record of having a highly developed medical service while at the same time also still lacking good health care access for its large number of subjects of low income. Lipid clinics are available in 6 teaching hospitals serving predominantly the indigent, but their services are available to all by referral.

These clinics have the authority to prescribe lipid modifying treatment, albeit on highly limited budgets, for lipid modifying agents.

The new South African government has embarked on a program of primary health care that is extending services into the previously poorly serviced communities. This is resulting in greater recognition of disorders such as FH and will contribute much to further understanding of this problem in the future. However, the developing health care is not actively making the diagnosis of FH, nor is it treating this disorder.

At present, as a crude estimate, about 10% of the citizens of the country have medical insurance, and another approximately 10% could afford preventive treatment for FH. These sectors contain almost a third of the FH burden but are facing problems with FH diagnosis and management. There are several reasons for the difficulties: There is still ignorance of this disorder at all levels of the health service. Medical insurance is becoming expensive, and medication is very expensive. Thus in the private health care sector as well as in the state health care sector serving the rest of the population, FH is not receiving the attention that it should.

The early diagnosis and early institution of treatment in FH would offer these subjects better quality and duration of life. Another consideration is that treatment of coronary artery disease, by medical or surgical means, is on offer to patients with FH and those who have lesser risk of atherosclerosis but still recognisably higher risk than the general population (e.g. diabetes, hypertension). In this setting it does not make sense to ignore preventive treatment.

It is notable that our health care programs consider the WHO recommendations for minimal/essential treatments to be important and base some of their decisions on these recommendations. It is thus expected that an official stand or even guideline from the WHO will help FH sufferers in our country. An alternative route of furthering the interests of subjects with FH is through other organisations. The Heart Foundation of South Africa has orientated itself to general educational and dietetic strategies and has not focused on FH. A lay body of patients, parents and interested parties has just set itself up as the Lipid Foundation to support the families of homozygous FH sufferers and to promote awareness and treatment of FH. The successful of such a movement in our trying economic times remains to be seen.

RECOMMENDATIONS
Recommendations of the South African MED-PED collaborators are integrated in the chapter 7 of the Report of the meeting.

Switzerland (Dr. Miserez):
In 1989, we started to systematically register patients with familial forms of hypercholesterolemia and to molecularly confirm or exclude low density lipoprotein (LDL) receptor defects in these patients and their relatives.

In 1994, we joined the International MED-PED FH Project. Although more than 67% of our cases with LDL receptor defects (familial hypercholesterolemia, FH) shared the four most common LDL receptor gene haplotypes detected in Switzerland, the molecular basis of FH appears to be extremely heterogeneous [48]. On the other hand, another disorder caused by defects in the apolipoprotein B-100 gene (familial defective apolipoprotein B-100, FDB), is highly prevalent in Switzerland [49]. In general, the phenotype of FDB is milder than that of FH [50]. Nevertheless, FDB may be - in particular in adults above forty years of age – clinically indistinguishable from FH [51]. FDB affects, in Switzerland, one in 210 individuals of the general population which is the highest prevalence reported world wide [49].

Thus, we routinely screen subjects with suggested familial forms of hypercholesterolemia first for mutations in the apolipoprotein B-100 gene (R3500Q and R3500W) and thereafter for mutations in the LDL-receptor gene. Another disorder which is causing elevated plasma cholesterol concentrations is familial dysbetalipoproteinemia (FDL). FDL is present in subjects homozygous for the R158C mutation in the apolipoprotein E gene and can easily be confirmed or excluded by molecular genetic analyses. Thus, our patients with familial forms of hypercholesterolemia are tested for FH and FDB as well as for FDL on a routine basis.

Currently, more than 4800 individuals, including 2276 control subjects, are registered. Approximately 3640 subjects (hyperlipidemic and controls) were molecular biologically screened for FDL and more than 3000 for the presence of FDB. The presence of LDL receptor gene mutations is tested by a non-radioactive, greatly improved, single strand conformation polymorphism (SSCP) method. Sequence variations in the LDL receptor gene are confirmed by subcloning of the respective gene fragment, SSCP of the clones, followed by DNA sequencing of the clones positive for the mutation.

Present and Future Significance of Molecular Genetic Testing in Familial Forms of Hypercholesterolemia.

Traditionally, heterozygous FH is diagnosed based on a two- to threefold elevation of plasma LDL cholesterol concentrations inherited in an autosomal-dominant fashion, the presence of premature coronary heart disease in the patient and other family members and specific lipid deposits in the tendons (tendon xanthomas).

LDL receptor defects cause a significant increase in plasma cholesterol which is detectable from birth [50]. In contrast, apolipoprotein B-100 mutations have been demonstrated to cause in childhood and early adulthood, often no or only moderate elevations of plasma cholesterol [50,53]. In Figure 1, cholesterol concentrations are shown in subjects with FH, FDB, and in controls from different age groups. In contrast to FH, in FDB subjects cholesterol levels are normal or only moderately elevated between birth and the age of forty years. Nevertheless, thereafter, plasma cholesterol concentrations tend to increase in FDB subjects and may reach the levels of FH patients [49]. Hence, if cholesterol is for the first time measured in a patient above forty years of age, the actual plasma cholesterol concentration does not necessarily reflect his or her true "cholesterol load" and thus, the risk to be affected by atherosclerotic lesions.

If the underlying defect is located at the LDL receptor locus, we have to assume that the patient has been exposed to significantly increased plasma cholesterol concentrations from birth and thus, in this case, during more than forty years.

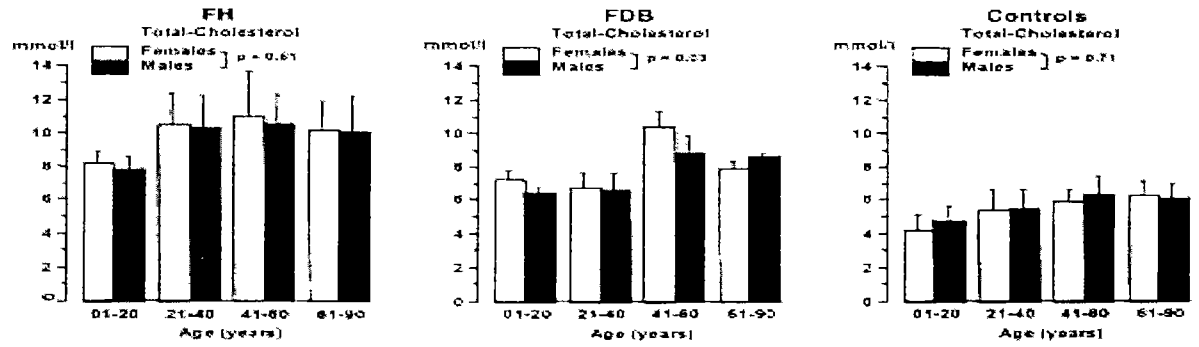

Figure 1: cholesterol levels in subjects with FH, FDB, and in controls from different age

On the other hand, if the defect is located at the apolipoprotein B locus, it is likely that the patient has been exposed for a much shorter time period to clearly elevated cholesterol levels while having for about thirty to forty years normal or only moderately increased plasma concentrations. Therefore, plasma cholesterol levels determined in subjects aged older than forty do not accurately predict the patient's risk of coronary heart disease. Thus, the additional information of the molecular diagnosis (FH versus FDB) would contribute to a better individual risk assessment.

Furthermore, in clinical practice, the identification of the underlying mutation helps us already today to rapidly and unequivocally identify affected family members and to exclude FH, FDB or FDL in non-affected individuals [54,55].Molecular genetic testing facilitates greatly our efforts in relatives of a patient with a known mutation to make early diagnosis of FH - the "MED"part of the MED-PED project [56,57]. In addition, in our experience, the confirmation of the diagnosis at the molecular level is a great help to motivate the patient to adhere to a cholesterol-lowering diet and to drug treatment ("PED"-part of the MED-PED). A recent study demonstrated that a majority (83%) of the individuals affected did not regret such tests confirming the diagnosis of FH [58]. These results are in perfect agreement with studies on molecular tests performed in diseases which are even more difficult to treat than FH, e.g. in colon cancer [59,60].

Differences in the phenotypic characteristics have not only been described between FH and FDB [50,53] but also between the different types of LDL receptor defects [60,61] and between the different apolipoprotein B defects [62]. Thus, the considerations made above for the differential diagnosis of FH versus FDB are applicable to the molecular differentiation of LDL receptor gene or apolipoprotein B gene defects as well.

New Techniques to Diagnose LDL Receptor Gene Defects

Whereas the exclusion or confirmation of FDB or FDL can be rapidly performed by polymerase chain reaction (PCR) based methods and subsequent restriction enzyme digestions, the confirmation or exclusion of LDL receptor defects is much more time-consuming. So far, more than 700 different LDL receptor defects in a coding sequence of only approximately 2500 base pairs have been described world-wide [63]. Furthermore, in most countries, the molecular basis of familial hypercholesterolemia appears to be extremely heterogeneous. Thus, new technologies to rapidly screen the entire coding sequence of the LDL receptor gene for known but also for new mutations need to be developed.