

NHLBI Clinical Trials

Introduction

The National Heart, Lung, and Blood Institute (NHLBI) has an extensive program of clinical trials dealing with critical issues in the prevention and treatment of heart, lung, and blood diseases. These contract programs now comprise about 9 percent of the NHLBI's extramural budget.

The investment in major clinical trials has grown since the early part of this decade to nearly \$42 million for fiscal year 1981 (table C-1).

NHLBI's complement of clinical trials represents a balance among several factors. First, the trial must be in NHLBI's purview; that is, the design and management of the clinical trial must require NHLBI's research expertise. Some validation studies may be aimed at questions that are related solely to health services delivery, and consequently such experiments would not fall within NHLBI's purview, although the Institute would very likely be involved in an advisory capacity.

Second, the clinical trial must satisfy several requirements related to such factors as the scientific basis for the trial's underlying hypothesis and the potential impact of that trial. Through NHLBI's experience with clinical trials, these factors have been incorporated into a clinical trial decision process that divides the trial into four distinct phases—initiation, planning, recruitment and intervention, and analysis and dissemination of the trial results. Separating each phase is a crucial decision point at which NHLBI de-

termines either to commit funds to the next stage of the clinical trial (the first two decision points) or to conclude the Intervention portion of the trial (the last decision point).

Tables C-2 and C-3 summarize data on the Institute's clinical trials. Table C-2 is a fiscal overview of the clinical trials, with the expected costs of the projects ranging from approximately \$1 million to over \$100 million. Table C-3 shows the broad characteristics of the clinical trials. The number of subjects ranges from very few—even as few as 100—up to almost **13,000** (for the Multiple Risk Factor Intervention Trial). The Institute's trials are currently in all phases of the clinical trial decision process; for example, the multicenter investigation of the limitation of infarct size (MILIS) is now in the recruitment and intervention phase, whereas the Hypertension Detection and Followup Program is in analysis and dissemination.

NHLBI's complement of clinical trials deals with both prevention of disease and treatment of disease. The primary prevention trials are testing interventions to prevent disease before biological onset; secondary prevention trials are testing intervention after the disease is detected but before it is symptomatic.

The following sections, taken from NHLBI's "Clinical Trials Briefing Document" (Jan. 27, 1982), summarize NHLBI's clinical trials program and are divided into: 1) recently completed trials; 2) recently initiated trials; and 3) trials in the planning stage.

Table C-1.

History of Major NHLBI Clinical Trials

(Dollars in Millions)

	FY 1972	FY 1973	FY 1974*	FY 1975	FY 1976†	FY 1977	FY 1978	FY 1979	FY 1980	FY 1981
Heart and Vascular Diseases										
HDFP	\$ 3.97	\$ 5.70	\$11.05	\$ 5.67	\$12.65	\$10.35	\$ 7.85	\$ 4.03	\$ 3.43	\$ 1.29
LRC	5.38	8.51	16.93	13.51	17.33	14.27	10.53	21.06	15.49	16.25
IMFIT	3.27	7.10	15.38	12.50	14.51	9.04	16.02	12.63	9.40	10.99
CASS	-	.10	.88	3.20	.87	2.85	4.59	1.78	4.44	2.40
AMIS	-	-	-	4.51	3.12	1.96	3.11	3.78	.37	-
BIAT	-	-	-	-	-	.54	3.72	5.99	3.85	3.80
MILIS	-	-	-	-	-	-	3.15	2.81	2.69	3.49
Subtotal,										
Heart and Vascular	12.62	51.41	44.24	39.40	48.48	39.01	48.97	52.08	3.67	38.31
Lung Diseases										
RDS Steroid Trials	-	-	-	-	.14	1.74	.32	1.49	.75	.45
Nocturnal Oxygen Therapy	-	-	-	-	.12	1.33	.91	1.24	.37	-
IPPB	-	-	-	-	-	.17	1.62	1.35	1.54	2.02
Subtotal, Lung Blood Diseases and Resources	-	-	-	-	.26	3.24	2.86	4.09	2.66	2.47
Factor VII Granulocyte Studies	-	-	-	1.27	.04	.75	.69	.38	-	-
	-	-	-	-	.30	.44	.36	.54	-	-
Subtotal, Blood	-	-	-	1.27	.35	1.19	1.05	.92	-	-
TOTAL NHLBI Major Clinical Trials	\$12.62	\$21.41	\$44.24	\$40.67	\$49.09	\$43.44	\$52.88	\$57.09	\$42.33	\$40.78

*Reflects release of fiscal year 1973 impounded funds.

†Includes Transition Quarter.

Note: Totals may not add due to rounding.

Source: National Heart, Lung, and Blood Institute.

Table C-2. Fiscal overview of NHLBI Clinical Trials

CLINICAL TRIAL	COST TO DATE*	PROJECTED TOTAL CoST
<u>Division of Heart and Vascular Diseases</u>		
Coronary Drug Project (CDP)	\$ 41,760,030	\$ 41,760,030
Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT)	86,727,695	104,420,695
Multiple Risk Factor Intervention Trial (MRFIT)	110,833,165	115,769,176
Hypertension Detection and Follow- up Program (HDFP)	68,174,982	70,541,982
Unstable Angina Pectoris Trial	485,849	485,849
Coronary Artery Surgery Study (CASS)	21,115,333	25,147,393
Program on Surgical Control of Hyperlipidemia (POSCH)	20,591,097	20,750,516
Aspirin Myocardial Infarction Study (AMIS)	16,859,386	16,859,386
Beta-Blocker Heart Attack Trial (BHAT)	17,985,327	18,200,000
Multicenter Investigation of Limitation of Infarct Size (MILIS)	12,568,841	19,437,341
Treatment of Hypertension	3,126,004	3,126,004
Management of Patent Ductus in premature Infants	4,120,095	4,120,095
Systolic Hypertension in the Elderly Program (SHEP)	2,036,251	3,550,000
Randomized Trial of Aspirin and Mortality in Physicians	506,002	2,372,155
Primary Prevention of Hypertension	1,121,387	10,933,260
Totals	\$408,011,504	465,474,382

*As of September 30, 1981.

Table c-2 (continued)

CLINICAL TRIAL	COST TO DATE*	PROJECTED TOTAL COST
<u>Division of Lung Diseases</u>		
Neonatal Respiratory Distress Syndrome	\$ 4,892,457	\$ 5,567,457
Intermittent Positive Pressure Breathing (IPPB)	6,718,975	9,532,975
Nocturnal Oxygen Therapy	3,977,382	3,977,382
Extracorporeal Membrane Oxygenator Study (ECMO)	5,552,340	5,552,340
Totals	\$ 21,141,154	\$24,630,154
<u>Division of Blood Diseases and Resources</u>		
Granulocyte Transfusion Study	\$ 1,635,142	\$ 1,635,142
Interruption of Maternal to Infant Transmission of Hepatitis B by Means of Hepatitis B Immune Globulin	113,711	113,711
Cooperative Study of Factor VIII Inhibitors	782,350	782,350
Hepatitis B Vaccine Clinical Trial	200,000	200,000
Totals	\$ 2,731,203	\$ 2,731,203

*As of September **30, 1981**

Table c-2 (continued)

CLINICAL TRIAL	COST TO DATE*	PROJECTED TOTAL COST
<u>Division of Intramural Research</u>		
NHLBI Type II Coronary Intervention Study	\$ 444,378	\$ 444,378
Diffuse Fibrotic Lung Disease	**	**
Evaluation of Subcutaneous Desferrioxamine as Treatment for Transfusional Hemochromatosis and a Controlled Trial on Ascorbic Acid	**	**
Totals	\$ 444,378	\$ 44,378
NHLBI Grand Totals	\$432,328,239	\$493,390,117

*As of September 30, 1981.

**The division of Intramural Research is reported in man-years, not dollars. The NHLBI Type II Coronary Intervention Study is also supported by a contract.

Source: National Heart, Lung, and Blood Institute

Table C-3.-Ongoing and Recently Completed
NHLBI Clinical Trials

CLINICAL TRIAL	SUBJECTS	STATUS	PROJECTED TOTAL COST
<u>Division of Heart and Vascular Diseases</u>			
Coronary Drug Project (CDP): Secondary prevention of coronary heart disease with cholesterol- lowering drugs.	8,341 subjects followed for 5 to 8.5 years at 53 clinics.	Initiated in 1965. Recruitment and Inter- vention completed in 1975. Now in Analy- sis and Dissemination Phase.	\$ 41,760,030
Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPT): Primary prevention of coronary heart disease in hypercholesteremic patients with the cholesterol- lowering drug cholestyramine.	3,810 subjects fol- lowed for 7 years at 12 clinics.	Now in the interven- tion phase, which is scheduled for comple- tion in 1983.	104,420,695
Multiple Risk Factor Intervention Trial (MRFIT): Primary prevention of coronary heart disease by lowering serum cholesterol, reducing blood pres- sure, and reducing or eliminating cigarette smoking.	12,866 subjects fol- lowed for 6 years at 20 clinics.	Now in the interven- tion phase, which is scheduled for comple- tion February 28, 1982.	115,769,176
Hypertension Detection and Follow-up Program (HDFP): Evaluation of hypertension control to reduce total mortality	10,940 subjects fol- lowed for 9 years at 14 clinics.	Now in the Analysis and Dissemination Phase.	70,541,982

Table C-3 (continued)

CLINICAL TRIAL	SUBJECTS	STATUS	PROJECTED TOTAL COST
Division of Heart and Vascular Diseases (Continued)			
<p>Unstable Angina Pectoris Trial: Secondary prevention of coronary heart disease by coronary artery bypass surgery or medical management in patients with unstable angina pectoris.</p>	288 subjects followed for 9 years at 9 clinics.	Now in the Analysis and Dissemination Phase, which is scheduled for completion in 1982.	\$ 485,849
<p>Coronary Artery Surgery Study (CASS): Treatment of coronary heart disease by coronary artery bypass surgery or medical management in patients with stable angina.</p>	780 subjects have been entered into this trial. Randomized patients to be followed for at least 4 years at 10 clinics. The study also includes a registry of 24,188 patients referred for coronary arteriography.	Recruitment ended in 1979. Follow-up is to extend for 5 years.	25,147,393
<p>Program on Surgical Control of Hyperlipidemias (POSCH): Prevention of myocardial infarction and death in survivors of myocardial infarction by partial ileo bypass surgery.</p>	Approximately 500 subjects have been recruited into this trial, which has a goal of 1,000 subjects. Patients are to be followed for 5 years at 4 clinics.	Now in the Recruitment and Intervention Phase.	28,500,515
<p>Aspirin Myocardial Infarction Study (AMIS): Prevention of myocardial infarction and death in survivors of myocardial infarction with the drug aspirin.</p>	4,524 subjects followed for 3 years at 30 clinics.	Now in the Analysis and Dissemination Phase.	16,859,386

Table c-3 (continued)


CLINICAL TRIAL	SUBJECTS	STATUS	PROJECT COST TOTAL COST
Division of Heart and Vascular Diseases (Continued)			
Beta-Blocker Heart Attack Trial (BHAT): prevention of myocardial infarction and death in survivors of myocardial infarction with the drug propranolol (a beta-blocker).	3,837 subjects followed for up to 3.5 Years at 32 clinics.	Now in the Analysis and Dissemination Phase.	
Multicenter Investigation of Limitation of Infarct Size (MILIS): Treatment of myocardial infarction with the drugs propranolol and/or hyaluronidase.	700 patients will be followed for 6 months in 5 clinics.	Now in the Recruitment and Intervention Phase, which is scheduled for completion in June, 1984.	19,437,941
Treatment of Hypertension: Primary prevention of cardiovascular morbidity and mortality by drug treatment of hypertension with <u>chlorothalazine plus  serpentina.</u>	389 subjects followed for up to 11 years at clinics.	Initiated in 1966. Recruitment and intervention Phase completed in 1976. Now in the Analysis and Dissemination Phase.	3,176,004
Management of Patent Ductus in Premature Infants: Comparison of treatment of patent ductus arteriosus with the drug indomethacin or with surgery and conventional medical therapy.	400 subjects to be followed at 12 clinics for 1 year.	in the Intervention Phase, which is scheduled for completion in March, 1982.	4,120,095
Systolic Hypertension in the Elderly Program (SHEP): Prevention of stroke with standard anti-hypertensive agents	500 subjects to be followed at 5 clinics.	Now in the Recruitment and Intervention Phase. Recruitment will continue throughout June, 1982. All patients are to be followed through June, 1983.	

Table C-3 (continued)

CLINICAL TRIAL	SUBJECTS	STATUS	INVESTIGATOR TOTAL COST
Division of Heart and Vascular Diseases (Continued)			
Randomized trial of Aspirin and Mortality in Physicians. Primary prevention of cardiovascular disease by daily administration of aspirin.	21,900 subjects to be followed for 4.5 years.	Now in the Planning Phase.	\$ 2,372, 55
Primary Prevention of Hypertension. Primary prevention of hypertension with low sodium, high potassium diet or weight reduction.	800 subjects to be followed for 2 years at 4 clinics.	Now in the Planning Phase.	10,933,260
Total DHVD			\$465,474,382

Tab e C-3 (continued)

CLINICAL TRIAL	SUBJECTS	STATUS	PRO E ED TOTAL COST
	<u>Division of Lung Diseases</u>		
Neonatal Respiratory Distress Syndrome: Primary prevention of neonatal respiratory distress syndrome by administering corticosteroids before birth.	696 subjects to be followed for 3 years in 5 clinics.	Now in the Follow-up Phase, which is scheduled for completion in March, 1983.	\$ 5,567,457
Intermittent Positive Pressure Breathing (IPPB): Treatment of chronic obstructive pulmonary disease with intermittent positive pressure breathing compared with powered nebulizer.	985 subjects are to be followed for 3 years in 5 clinics.	Now in the the Interventions Phase, which is scheduled for completion in 1983.	9,532,975
Hyperbaric Oxygen Therapy: Treatment of chronic hypoxic lung disease with 12-hour oxygen therapy compared with continuous low-flow oxygen therapy.	203 subjects followed for up to 30 months in 6 clinics.	Recruitment and Intervention completed in 1979. The trial has concluded.	3,977,382
Extracorporeal Support for Respiratory Insufficiency (ECMO): Treatment of acute respiratory failure with an extracorporeal membrane oxygenator.	90 subjects were followed for at least 5 days in 9 clinics.	Initiated in 1974. The Recruitment and Intervention Phase was completed in 1977. The trial has concluded.	5,552,340
		Total 1979	\$ 24,630,154

Table C-3 (continued)

CLINICAL TRIAL	SUBJECTS	STATUS	PROJECTIONS	
			O A	NS
Division of Blood Diseases and Resources				
Granulocyte Transfusion Study: Primary prevention and treatment of infection in patients undergoing chemotherapy for leukemia.	147 subjects followed for 3 years in 4 clinics.	Recruitment and Intervention ended in February 1980. Now in the Analysis and Dissemination Phase.	\$	1,635,142
Interruption of Maternal-to-Infant Transmission of Hepatitis B by Means of Hepatitis B Immune Globulin: Prevention of hepatitis B in infants.	205 subjects were followed for 3 years in 1 clinic.	Initiated in 1975. The Recruitment and Intervention Phase was completed in 1978. The trial is now complete.		113,711
Cooperative Study of Factor VIII Inhibitors: Factor IX treatment of persons with hemophilia A and inhibitors to Factor VIII.	51 subjects followed for varying lengths of time in 10 clinics.	The Intervention Phase was completed in late 1979. The trial has concluded.		782,350
Hepatitis B Vaccine Clinical Trial Vaccination of susceptible subjects with a vaccine which prevented hepatitis B	1083 subjects followed for 2 years.	Initiated in 1978. Recruitment completed in October 1979. The trial has concluded.		200,000
Total DBDR			\$	2,731,203

Table C-3 (continued)

CLINICAL TRIAL	SUBJECTS	STATUS	PROJECTED TOTAL COST
<u>Division of Intramural Research</u>			
NHLBI Type II Coronary Intervention Study: Evaluation of lowering cholesterol with the drug cholestyramine in Type II hyperlipidemics in coronary artery disease regression.	143 subjects followed for 5 years at 1 clinic.	Now in the Analysis and Dissemination Phase which is scheduled for completion in 1982.	\$ 443,378*
Diffuse Fibrotic Lung Disease: Treatment of idiopathic pulmonary fibrosis with cyclophosphamide compared with prednisone, or with dapsone or methylprednisolone. Treatment of sarcoidosis with short-term, high dose intravenous corticosteroids.	Approximately 150 subjects followed for up to 1 year at 1 clinic.	Now in the Intervention Phase.	**
Evaluation of Subcutaneous Desferrioxamine as Treatment for Transfusional Hemochromatosis: Treatment of iron-overload with the agent desferrioxamine and ascorbic acid.	65 eligible subjects followed for up to 5 years at 2 clinics.	Now in the Recruitment and Intervention Phase.	**
	Total DIR		\$ 444,378
	Total NHLBI		\$493,280,117

*Contract costs only. Does not include Division of Intramural Research cost.

**The Division of Intramural Research is reported in man-years, not dollars.

Source: National Heart, Lung, and Blood Institute

II. Recently Completed Trials

HYPERTENSION DETECTION AND FOLLOW-UP PROGRAM (HDFP)

Objective

To determine the **effectiveness of systematic**, sustained, antihypertensive therapy in reducing morbidity and mortality from hypertension in a wide spectrum of persons with elevated blood pressure in 14 communities. During its course, the trial also obtained a direct measure of prevalence, severity, and current treatment status of representative white and black populations with high blood pressure in these 14 communities, and **obtained an estimate of the extent** of attainable reduction of complications of high blood pressure by an organized screening and blood pressure management program.

Summary Data

Mechanism:	Contract (Institute Initiated Clinical Trial)	
Initiation:	May 1971	
Total Duration:	11 years (Intervention and Follow-up: 9 years)	
Funding:		
	Total Support Prior to FY 1981	\$66,890,877
	FY 1981 support	1,284,105
	Support Projected Beyond FY 1981	2,367,000
	Total Support	<u>70,541,982</u>

Hypertension Detection and Follow-up Program (HDFP)

Background

Published data from the Veterans Administration Cooperative Study of Hypertension demonstrated that reduction in morbidity and mortality could be attained by treating men with fixed diastolic blood pressure over 105 mm Hg. Similar trends occurred for those with fixed diastolic blood pressure between 90 and 104 mm Hg. Results and current trends from other studies supported these findings. However, Prior to inception of the Hypertension Detection and Follow-up Program (HDFP), it was not known whether benefits from anti hypertensive therapy applied to all hypertensives in the general population and whether making use of existing medical knowledge could significantly reduce morbidity and mortality from hypertension in communities.

Recognizing this need, NHLBI initiated the pilot activities of the HDFP to characterize Significant Operational, socioeconomic, and motivational or behavioral factors that would influence the acceptance of antihypertensive therapy in the defined populations within which the controlled clinical trial would take place and to obtain baseline information necessary to the undertaking of the clinical trial.

The planning of the trial, including the development of a protocol and manual of operations, began in 1971. Between February 1973 and May 1974, 158,906 persons were screened for high blood pressure in 14 communities. A total of 10,940 hypertensive participants were randomized.

The primary hypothesis tested by this clinical trial was that intensive blood pressure control under stepped care for 5 years can significantly reduce mortality compared with that under referred care. Stepped care is the method of treatment in HDFP clinics in which a diuretic is given initially and additional antihypertensive agents are added in a time-structured, stepwise fashion until goal blood pressure is achieved. Referred care represents referral to private physicians and other community sources of care. Participating in this study were 14 clinical centers, a coordinating center, EKG center, central laboratory, and monitoring laboratory.

The intervention portion of the trial has been completed. The study is being extended through May 1982 in order to continue the surveillance of mortality and blood pressure control.

Trial Results

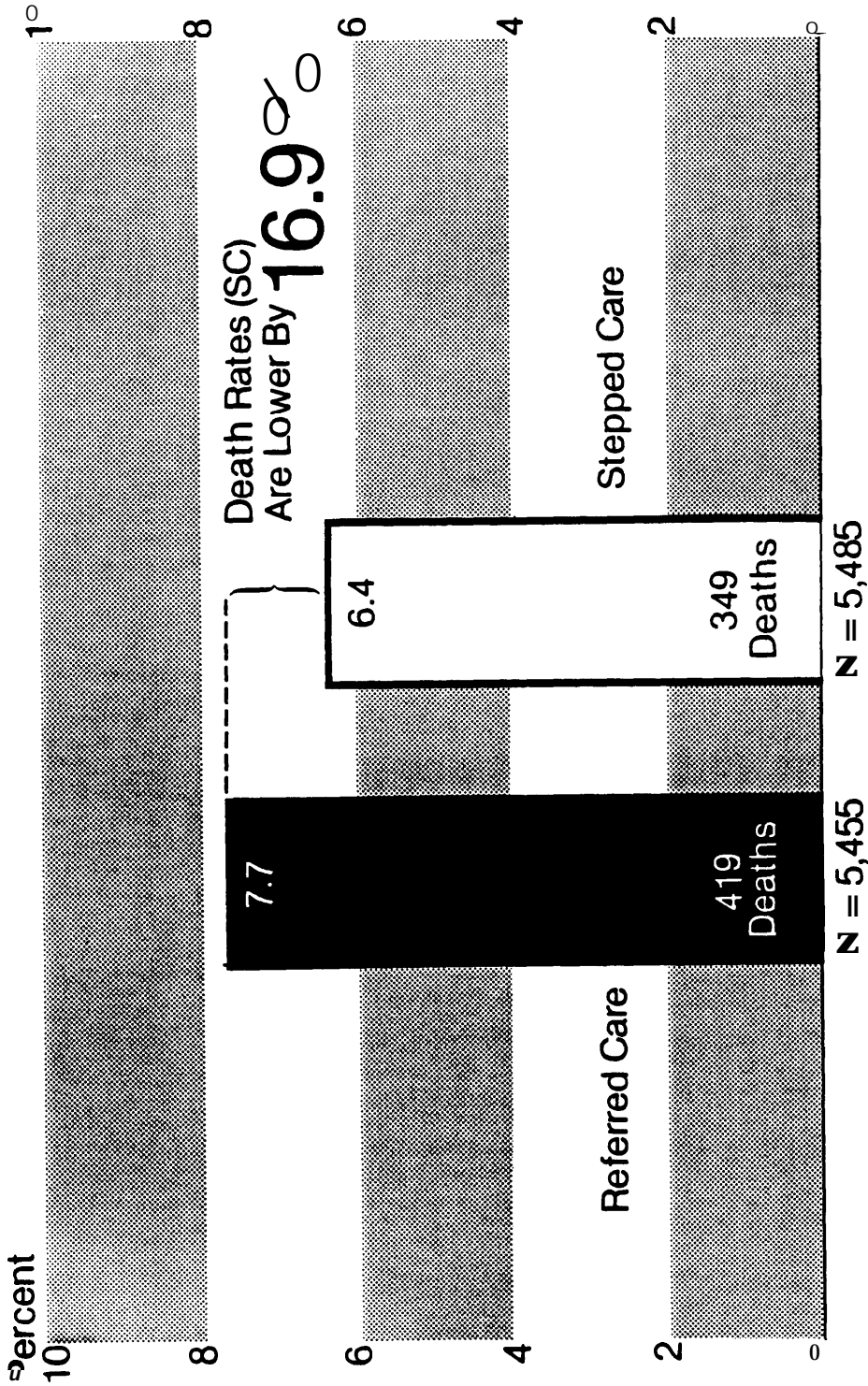
The following statements have been abstracted from papers appearing in the Journal of the American Medical Association.*

- 0 Five-year mortality from all causes was 17 percent lower for the stepped-care group compared with the referred-care group (see Figure 3) and 20 percent lower for the stepped-care participants with "mild" hypertension (diastolic blood pressure 90-104 mm Hg compared with the corresponding referred-care subgroup).

Figure C-1. ---

Mortality - All Causes

5-Year Mortality Rates (%) From All Causes for Stepped Care (SC) and Referred Care (RC) Participants



Hypertension Detection and Follow-up Program (HDFP)

- 0 Preliminary data on cause-specific mortality indicate that the number of deaths from Cerebrovascular disease was smaller by almost 45 percent for the stepped-care group. There were 26 percent fewer deaths from acute myocardial infarction in the stepped-care group. Death rates from other ischemic heart disease were similar in both groups. Nine deaths in the stepped-care group were certified to **hypertension** compared with 14 in the referred-care group. For all cardiovascular causes, there were 19 percent fewer deaths for the *stepped-care* group than for the referred-care group.
- 0 For white men, black men, and black women and for age subgroups 50 to 59 and 60 to 69, 5-year all-cause death rates were substantially lower--by 15 percent to 28 percent--for the stepped-care subgroups compared with the referred-care subgroups.
- 0 Blood pressure control was consistently better for the stepped-care group than for the referred-care group. After 5 years, 64.9 percent of the stepped-care participants had reached goal diastolic blood pressure versus 43.6 percent of the referred-care participants. Goal diastolic blood pressure was defined as 90 mm Hg for those entering with DBP equal to or greater than 100 or receiving anti hypertensive therapy, and a 10 mm Hg decrease for those entering with DBP 90-99. After 5 years, 63.8 percent of those stepped-care participants in stratum I (DBP 90-104) achieved goal diastolic blood pressure versus 43.0 percent of those in referred-care. Also, after 5 years, 69.6 percent of stepped-care participants in stratum II (DBP 105-114) achieved goal diastolic blood pressure versus 48.3 percent of those in referred-care and 63.6 percent of stepped-care participants in stratum III (DBP 115 or higher) achieved goal diastolic blood pressure versus 39.1 percent of referred-care participants.
- 0 Systematic, effective management of hypertension has great potential for reducing mortality for the large numbers of people with hypertension in the population, including those with "mild" hypertension.

~~*Hypertension Detection and Follow-up Program Cooperative Group:~~

Five-year Findings of the Hypertension Detection and Follow-up Program: I. Reduction in Mortality of persons with High Blood Pressure, Including Mild Hypertension. JAMA 242:2562-2571, 1979.

Hypertension Detection and Follow-up Program Cooperative Group:

Five-Year Findings of the Hypertension Detection and Follow-up program: II. Mortality by Race-sex and Age. JAMA 242:2572-2577, 1979.

ASPIRIN-MYOCARDIAL INFARCTION STUDY (AMIS)

Objective

To determine whether the daily administration of 1 gm of aspirin to individuals with a documented myocardial infarction will result in a significant reduction in mortality over a 3-year period.

Summary Data

Mechanism:	Contract (Institute Initiated Clinical Trial)	
Initiation:	October 1974	
Total Duration:	6 years (Intervention: minimum 3 years)	
Funding:		
Total Support Prior to FY 1981	\$16,859,386	
FY 1981 Support	0	
Support Projected Beyond FY 1981	0	
Total Support	\$16,959,386	

Subjects

Males and females, ages 30-69, not stratified as to ethnic groups with a documented myocardial infarction.

Experimental Design

Randomized, double-blind, fixed sample. Eligible patients were assigned to a treatment group receiving 1 gm of aspirin daily (the equivalent of three standard aspirin tablets) or to a control group receiving a placebo.

Current Phase (As of October 1981): Analysis and Dissemination

Background

It has been postulated that thrombosis plays a major role in the late stages of coronary artery occlusion. Platelet aggregation is a large component in the formation of arterial thrombi. Theoretically, an agent which prevents the aggregation of platelets would be of value in people with coronary artery disease. Aspirin, in small doses, inhibits platelet aggregation for prolonged periods of time, and therefore might be expected to prevent or retard the occlusion of coronary arteries. This would be reflected in a decrease in the incidence of myocardial infarction and a decrease in mortality due to coronary artery disease.

Several studies had given preliminary evidence that regular administration of aspirin may be of benefit to patients with known the Coronary Drug Project, ran a pilot trial of aspirin and placebo in men with previous myocardial infarctions. Preliminary results from this trial demonstrated its feasibility and led NHLBI to sponsor a more definitive controlled study of the benefit of aspirin in the secondary prevention of coronary heart disease.

Aspirin-Myocardial Infarction Study (AMIS)

An Institute Planning Committee developed a protocol, manual of operations, and data collection forms. Recruitment of patients began in June 1975, with the first patient randomized on July 2, 1975. Patients who were randomized had been seen at the **AMIS** Clinical Center for two initial visits and one baseline visit and were free of any reasons for exclusion, such as the current use of anticoagulants **and** a history of adverse reactions to aspirin. Patients took acetaminophen at times when they would normally take aspirin.

Follow-up was for a minimum of 3 years, with each patient seen at 4-month intervals and monitored for side effects and various nonfatal events, including cardiovascular problems. The primary endpoint was mortality. Annually, a detailed history was obtained and a complete physical examination performed. The study involved 30 clinical centers, a coordinating center, and a central **laboratory**.

The study completed patient recruitment in the scheduled 1-year period. A total of 4,524 post-MI patients were enrolled by the 30 clinical centers. Three-year minimum patient follow-up ended in June 1979.

Trial Results

- 0 Total mortality during the entire follow-up period was 10.8 percent in the aspirin group and 9.7 percent in the placebo group.
- 0 Three-year mortality was 9.6 percent in the aspirin group and 8.8 percent in the placebo group.
- 0 The rate of definite nonfatal MI was 8.1 percent in the placebo group and 6.3 percent in the aspirin group.
- 0 Coronary incidence (coronary heart **disease** mortality or definite nonfatal **MI**) was 14.1 percent in the aspirin group and 14.8 percent in the placebo group.
- 0 Symptoms of peptic ulcer, gastritis, or erosion of gastric mucosa occurred in 23.7 percent of the aspirin group and 14.9 percent of the placebo group.
- 0 Based on AMIS results, aspirin is not recommended for routine use in patients who have survived a myocardial infarction.

BETA-BLOCKER HEART ATTACK TRIAL (BHAT)

Objective

To determine whether the regular administration of the beta-blocker drug propranolol to people who have had at least one documented myocardial infarction will result in a significant reduction of mortality from all causes over the follow-up period. A total of 3,837 eligible volunteer patients were recruited to participate in a double-blind clinical trial within 5 to 21 days after the onset of the acute event. One-half of the patients were randomly assigned to a beta-blocking drug (propranolol) and one-half to a placebo. The trial also evaluated the effect of propranolol on incidence of coronary heart disease mortality, sudden cardiac death, and nonfatal myocardial infarction plus coronary heart disease mortality in persons with documented previous myocardial infarction.

Summary Data

Mechanism:	Contract (Institute Initiated Clinical Trial)	
Initiation:	September 1977	
Total duration:	7 years (Intervention: 1-3.5 years)	
Funding:		
	Total Support Prior to FY 1981	\$14,098,633
	FY 1981 Support	3,886,694
	Support Projected Beyond FY 1981	214,673
	Total Support	<u>18,200,000</u>

Subjects

Males and females, ages 30-69, who have had at least one myocardial infarction. Subjects were not stratified as to ethnic group and were drawn from various locations in the United States. Total sample size equaled 3,837. Individuals were randomized to treatment and control groups.

Experimental Design

A randomized, double-blind design with single experimental and control groups. Patients were recruited while in the hospital for an acute myocardial infarction and enrolled in the study before discharge. Eligible patients fulfilled the study definition of an acute myocardial infarction. The diagnosis was based either on electrocardiographic records showing evolving QRS segment changes or on ST segment and T wave changes together with enzyme changes and appropriate clinical history. One-half of the patients were placed on therapy using a beta-blocking drug (propranolol). The other half received a placebo. **Intervention duration was 1-3.5 years.**

Current Phase (As of October 1981): Analysis and Dissemination

Beta Blocker Heart Attack Trial (BHAT)

Background

Coronary heart disease and its complications account for over 600,000 deaths in the U.S. each year. Survivors of a documented myocardial infarction are recognized as having a high risk of dying relative to the general population. Serious arrhythmias, occurring with or without evidence of new infarction, are a common cause of death in this population. Theoretically, an agent which (1) can block the sympathetic nervous activity thought to be involved in precipitating sudden death and (2) has non-neurogenic antiarrhythmic properties would be of value to people with coronary heart disease. Propranolol, like other beta-blocking agents, has these as well as other properties and therefore might be expected to prevent or retard complications of coronary heart disease such as serious arrhythmias. This would be reflected in a decrease in mortality due to coronary heart disease.

A workshop on chronic antiarrhythmic therapy held in 1976 reviewed contemporary experimental data and clinical practice and recommended that a clinical trial be undertaken to clearly show the effects of beta-blocking drugs on mortality. **Subsequently, such a trial was** approved by the Clinical Applications and Prevention Advisory committee, by the Cardiology Advisory Committee, and by the National Heart, Lung, and Blood Advisory Council.

The study protocol was reviewed in February 1978 and recommended for approval by the policy-data monitoring board and ad hoc members. The protocol was approved by the Director of NHLBI in March 1978. Recruitment started on June 19, 1978 and ended in October 1980. A total of 3,837 patients were randomized. Participating in the trial were 32 clinical centers, an EKG center, a central laboratory, a coordinating center, a 1-hour ambulatory EKG center, a 24-hour ambulatory EKG center, and an EKG tape quality control center.

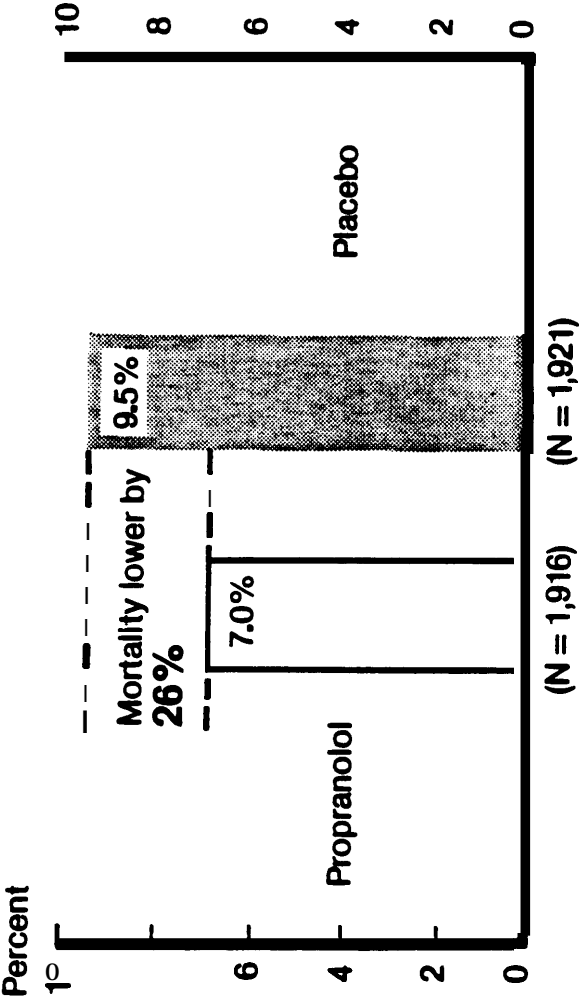
Trial Results

On the recommendation of the Policy and Data Monitoring Board, intervention **was** ended in October 1981 instead of in June 1982. Mortality was 9.5% in the placebo group and 7.9% in the propranolol group, a reduction of 26% (see Figure 4). Preliminary results of the trial indicate that the beneficial effects of propranolol occur primarily in the first year after a myocardial infarction.

Figure 5

Beta Blocker Heart Attack Trial

TOTAL MORTALITY
(Average 24 Month Follow up)



PREVENTION OF NEONATAL RESPIRATORY DISTRESS SYNDROME
WITH ANTENATAL STEROID ADMINISTRATION

Objective

To determine the effect of corticosteroids, administered 24 to 48 hours before parturition, on the incidence of neonatal respiratory distress syndrome (RDS) and to determine whether the therapy has any adverse short- or long-term (up to 36 months) effects on the infant. Secondly, to determine whether the therapy **has any adverse short-term** effects on the mother and to determine whether morbidity rates for neonatal respiratory distress syndrome **as** well as total and cause-specific infant mortality rates differ between mothers who received antenatal steroids and those who received conventional medical care.

Summary Data

Mechanism:	Contract (Institute Initiated Clinical Trial)	
Initiation:	June 1976	
Total Duration:	6 years (Intervention: 48 hours; Follow-up: 36 months)	
Funding:		
	Total Support Prior to FY 1981	\$4,438,366
	FY 1981 Support	454,091
	Support Projected Beyond FY 1981	675,000
	Total Support	<u>\$5,567,457</u>

Subjects

Male and female fetuses and infants; **pregnant** women with anticipated premature delivery and gestational age between 26 and 37 weeks.

Experimental Design

Randomized, double-blind, fixed sample. Six hundred and ninety-six patients were randomized to four doses of dexamethasone every 12 hours or to placebo. Endpoints were the incidence of respiratory distress syndrome and abnormality of motor-neuro-intellectual development.

Current Phase (As of October 1981) Intervention (Follow-up)

Background

Neonatal respiratory distress syndrome is one of the leading causes of disability and death in the newborn. In the United States, approximately 10 percent of all infants are premature, and each year about 50,000 cases of neonatal respiratory distress syndrome occur. Hospital costs at the onset of the trial averaged \$5,000 per patient, with an average stay of 23 days.

Prevention of Neonatal Respiratory Distress Syndrome with Antenatal Steroid Administration

Extensive studies in animal models on respirator distress syndrome have demonstrated that antenatal administration of synthetic (dexamethasone) and natural (cortisol) corticosteroids accelerates lung maturation and significantly diminishes the occurrence of RDS. Only one large, controlled, double-blind clinical trial on antenatal corticosteroid therapy has been published to date, although this therapy is beginning to be widely used in the United States. **In that trial**, which was conducted in New Zealand, it was reported that there is a lower-than expected incidence of neonatal RDS when betamethasone is given to mothers for at least 24 hours after the onset of premature labor and not later than the 32nd week of gestation. No follow-up data, however, have been published. **Although a variety of conditions in newborn infants have been treated with steroids over the past 20 years without adverse effects, investigations have been needed on the short-term effects of corticosteroids administered antenatally on neonate and mother and on the long-term effects on the infants.**

The Planning Phase of this trial **was** completed in March 1977, with formulation of a common protocol and manual of operations. Patient screening and enrollment began in May 1977 and ended on March 1, 1980. Follow-up will continue for 36 months after the entrance of the last patient. At the present time, there are five clinical centers and a coordinating center in the trial.

Preliminary Trial Results

Fetal and neonatal death rates were not significantly altered by treatment. Fetal death rate was 1.6% in the treatment group and 2.2% in the placebo group. Neonatal death rate before 40 weeks of age was 9.3% in the treatment group and 8.8% in the placebo group. The overall incidence of RDS **was** different between control subjects (18.0%) and **treated mothers (12.6%)**. This effect **was** mainly due to the pronounced beneficial effect of treatment on singleton **female** infants. No treatment effect was observed in male infants. Non-Caucasians were improved, whereas Caucasians showed little benefit.

CORONARY DRUG PROJECT

Objective

To determine whether the regular administration of lipid modifying drugs (clofibrate, nicotinic acid, estrogen, dextrothyroxine) to men with a documented myocardial infarction would result in significant reduction in total mortality over a 5-year period. Secondly, to determine whether the degree to which these drugs change serum lipids is correlated with any effect on mortality and morbidity rates; to gain further information on the long-term prognosis of myocardial infarction (by studying the control group as intensively as the treatment group); to acquire further experience and knowledge concerning the techniques and methodology of long-term clinical trials; to determine, in a substudy, the effectiveness of aspirin, a platelet inhibitor, in reducing recurrences of myocardial infarction.

Summary Data

Mechanism:	Grant (Investigator Initiated Clinical Trial)
Initiation:	April 1965
Total Duration:	16 years (Intervention: 5-8.5 years*)
Funding:	
Total Support Prior to FY 1981	\$41,590,050
FY 1981 Support	169\$980
Support Projected Beyond FY 1981	0
Total Support	\$41,760,030

Subjects

Males, ages 30-64, not stratified as to ethnic group, who were 3 months beyond their most recent myocardial infarction.

Experimental Design

Randomized, double-blind, fixed sample. A **total** of 8,341 patients were randomly assigned to six treatment groups consisting of 2.5 mg/day of conjugated estrogens, 5.0 mg/day of conjugated estrogens, 1.8 gm/day of clofibrate, 6.0 mg/day of dextrothyroxine sodium, 3.0 gin/day of niacin, or 3.8 gin/day of lactose placebo.

Current phase (As of October 1981): Nearly concluded, small Analysis and Dissemination effort underway.

Background

Correlation of high levels of serum cholesterol with an increased incidence and prevalence of coronary heart disease (CHD) was demonstrated--prior to the inception of the Coronary Drug Project--repeatedly in prospective and cross-sectional epidemiological surveys (e.g., the Tecumseh Study, the Framingham Heart Disease Study). These findings led to the question of

*Applies to clofibrate and niacin therapy. Estrogen and dextrothyroxine treatments were discontinued early.

Coronary Drug Project

whether long-term lowering of serum lipids in individuals both with and without CHD would have a beneficial effect on morbidity and mortality. The Coronary Drug Project was designed to answer the question of secondary prevention. In 1961, Dr. Robert Wilkins (Boston University School of Medicine) chaired an ad hoc committee which determined the desirability and feasibility of the conduct of this study. Following National Heart Advisory Council (NHAC) support, a study Policy Board, Steering Committee, and Coordinating Center were established and a detailed protocol was written. In 1964, NHAC approved the project and the NHI recommendation for implementation; the study was begun in 1965. Supported by the grant mechanism, the trial involved 53 participating clinics, a coordinating center, central laboratory, ECG center, drug procurement and distribution center, and NHI medical liaison office, and a policy board, steering committee, and 12 other committees (e.g., a data and safety monitoring committee).

The first patient was randomly allocated to treatment in March 1966 and the last in October 1969. Each patient reported to the clinic every 4 months for a follow-up visit,

Trial Results

Three drug regimens were discontinued before the scheduled completion of the project. The 5.0 mg/day estrogen regimen was discontinued in 1970 because of the number of nonfatal cardiovascular events when compared with placebo and lack of evidence of efficacy with respect to the primary endpoint of total mortality. Dextrothyroxine sodium was discontinued in 1971 because of excess mortality in the treatment group as compared with the placebo group. The third regimen 2.5 mg/day of estrogen, **was** discontinued in 1973.

Findings in the nicotinic acid and clofibrate treated groups were that

- 0 both drugs produced modest reduction in serum cholesterol concentrations,
- 0 neither significantly decreased mortality compared with that of patients receiving placebo, and
- 0 both drugs were associated with unpleasant and hazardous side effects* which affected both the cardiovascular and digestive systems.

These negative findings refer only to secondary prevention--to patients who **have** had one or more previous heart attacks--and do not indicate whether either clofibrate or nicotinic acid is useful for individuals who have not had a heart attack (i.e., for primary prevention).

*Clofibrate was associated with a high degree of cardiovascular morbidity. Nicotinic acid decreased angina and new heart attacks, but was associated with frequent side effects.

Coronary Drug Project

The study was extremely worthwhile in several respects:

- 0 The trial established the hazardous side effects of the lipid-lowering drugs. Side effects might still be attributed to the natural course of the disease rather than to the drugs.
- 0 The information obtained on the natural history of myocardial disease is extremely valuable and useful.

The trial also serves as the foundation for the primary prevention trials now underway.

The vital status as of March 1, 1980 of all Participants alive at the end of the Coronary Drug Project is currently being examined. The objective is to confirm or refute reports of continued adverse effects on mortality of clofibrate years after cessation of use OF the drug. This mortality surveillance will be conducted from June 1981 - June 1982 by the Coordinating Center.

UNSTABLE ANGINA PECTORIS TRIAL

Objective

To compare the efficacy of medical or surgical (coronary artery bypass graft) therapy with regard to survival and quality of life in patients with unstable angina and requisite coronary anatomy as defined by angiography.

Summary Data

Mechanism:	Contract and Grant (Institute Initiated Clinical Trial)	
Initiation:	January 1972	
Total Duration:	10 years (Intervention: 2 years)	
Funding:		
	Total Support Prior to FY 1981	\$485,849
	FY 1981 Support	0
	Support Projected Beyond FY 1981	0
	Total Support	\$485,849

Subjects

Males and females, ages 21 to 65, from selected sites across the United States. All subjects had class **III** or **IV** angina pectoris in which pain occurred at rest or with minimal exercise.

Experimental Design

Randomized, non-blind, sequential design with a control group and an experimental group. The patients in the experimental group were treated with coronary bypass surgery. Patients in the control group received intensive medical management. Endpoints were mortality and morbidity measures, such as incidence of myocardial infarction and persistence of angina.

Current Phase (As of October 1981): Analysis and Dissemination

Background

Angina pectoris is a symptomatic condition of attacks of chest pain, often debilitating. It is caused by a decreased supply of blood to the heart, such as that which might occur in coronary artery disease. The usual treatment of angina pectoris is designed to relieve the symptoms. It includes avoidance of activities that produce the discomfort **and the use** of nitroglycerin and beta-blocking drugs. Soon after the introduction of coronary bypass surgery, many doctors enthusiastically adopted this approach in treating patients with unstable angina.

In 1972, emphasizing that there was no definitive evidence showing the superiority of intensive medical management or coronary bypass surgery in determining mortality and morbidity in patients hospitalized with unstable angina, some of the participating groups in the NHLBI Myocardial Infarction Research Units developed a cooperative clinical trial to compare these medical and surgical approaches to therapy.

Unstable Angina Pectoris Trial

From 1972 through 1976, 288 patients were entered into this randomized clinical trial. One hundred forty-seven patients received intensive pharmacological medical therapy, and 141 comparable patients underwent coronary artery bypass surgery. Careful follow-up studies were performed on patients in both groups, in-hospital and during the post-hospital phase. These studies included, apart from routine physical examinations, resting electrocardiograms, chest x-ray films, and grade exercise tolerance tests at six months and twelve months.

Unstable Angina Pectoris Trial

Trial Results

During the study period, the hospital mortality rate was 5 percent in the surgical group and 3 percent in the medical group (difference not significant). * The rate of in-hospital myocardial infarction was 17 and 8 percent in the respective groups ($P < 0.05$). In the last 4 years of the study (1973 to 1976), the hospital mortality rate decreased to 3 percent in the surgical group and to 2 percent in the medical group (difference not significant). During the last 3 years of the study (1974 to 1976), the rate of in-hospital myocardial infarction was 13 percent in the surgical group and 10 percent in the medical group (difference not significant). There were no differences in the subsets of patients with one-, two-, or three-vessel disease.

In the first year after hospital discharge, class III or IV angina (New York Heart Association criteria) was more common in medically than in surgically treated patients with one-vessel disease (22 percent versus 3 percent, $P < 0.05$), two-vessel disease (40 percent versus 13 percent, $P < 0.01$), and three-vessel disease (40 percent versus 15 percent, $P < 0.01$). During an average follow-up period of 30 months, 36 percent of the medically treated patients later underwent surgery to relieve unacceptable angina. Late mortality was comparable in the two groups, but the large number of medically treated patients who later underwent surgery prevents definitive conclusions about the relative effect of medical and surgical therapy on long-term mortality. However, the patients who responded to medical therapy did not have a higher rate than surgical patients.

The results indicate that patients with unstable angina pectoris can be managed acutely with intensive medical therapy, including the administration of propranolol and long-acting nitrates in pharmacologic doses, with adequate control of pain in most patients and no increase in early mortality or myocardial infarction rates. Later, elective surgery can be performed with a low risk and good clinical results if the patient's angina fails to respond to intensive medical therapy.

* Unstable Angina Pectoris Study Group: Unstable Angina Pectoris National Cooperative Study Group to Compare Medical and Surgical Therapy. II. In-Hospital Experience and Initial Follow-up Results in Patients with One-, Two-, and Three-Vessel Disease. Am. J. Cardiol. 42: 839-848, 1978.

NOCTURNAL OXYGEN THERAPY

Objective

To compare the efficacy of long-term use of nocturnal oxygen therapy (12 hours) with that of continuous, low-flow oxygen therapy (24 hours) in patients with chronic hypoxic lung disease.

Summary Data

Mechanism:	Contract (Institute Initiated Clinical Trial)	
Initiation:	July 1976	
Total Duration:	4 years	
Funding:		
	Total Support Prior to FY 1981	\$3,977,382
	FY 1981 Support	0
	Support Projected Beyond FY 1981	0
	Total Support	<u>\$3,977,382</u>

Subjects

Males and females, ages 35-70, not stratified as to ethnic group, who have severe chronic obstructive lung disease requiring supplemental oxygen therapy.

Experimental Design

Randomized, fixed sample. Two hundred and three patients were randomly assigned to at-home treatments of continuous oxygen therapy or nocturnal oxygen therapy. Endpoints related to quality of life, neuropsychological function, and respiratory function and capacity. Intervention lasted for 6 months to 3 years, with an average intervention of 19.3 months.

Current Phase (As of October 1981); Concluded

Background

Chronic obstructive pulmonary disease is a major health problem in the United States. In 1975, it **was** the sixth leading cause of death. The economic impact of the disease in 1972 amounted to \$803 million in the direct costs of disability treatment, \$3.05 billion in disability costs, and \$645 million in lost earnings due to premature death.

Motivated in part by the significant toll of this disease, a conference on the Scientific Basis of Respiratory Therapy, co-sponsored by the American Thoracic Society and the Division of Lung Diseases, examined the current status of the use of oxygen therapy in chronic lung disease. The proceedings of the conference, published in the American Review of Respiratory Disease (Vol. 110, No. 6, December 1974), included a recommendation for clinical studies that would provide a critical assessment of the role of nocturnal oxygen therapy in the treatment of patients with chronic obstructive pulmonary disease. Low-flow oxygen, administered continuously, is known to benefit some patients with chronic hypoxic lung disease. However, low-flow oxygen administration for long

Nocturnal Oxygen Therapy

periods of time is cumbersome, confining, **and** expensive. If nocturnal oxygen administration could be unequivocally demonstrated to be efficacious, then the advantages of convenience and cost would have a favorable impact on treatment of patients, and a rationale could be developed for testing this therapy in a larger group of patients.

The Planning Phase of the trial was initiated in September 1976. Patient recruitment began in May 1977. The Recruitment Phase lasted 24 months. The 203 patients in the trial were assigned randomly to home treatments with nocturnal oxygen therapy or continuous low-flow oxygen therapy. The Recruitment and Intervention Phase has ended. The trial has now concluded.

Trial Results

Mortality in the nocturnal oxygen therapy group was nearly twice that in the continuous oxygen therapy group.* Sixty-four patients died, 41 in the nocturnal oxygen therapy group and 23 in the continuous oxygen therapy group. The 12-month mortality rate was 20.6 percent in the nocturnal oxygen therapy group and 11.9 percent in the continuous oxygen therapy group; 24-month mortality was 40.3 percent and 22.4 percent, respectively. Overall mortality was 31.5 percent for all patients.

The reason for the decreased mortality associated with continuous oxygen therapy is unclear. Only two of the numerous physiological and psychological variables showed a significant treatment-related change with time. Hematocrit value decreased in patients on continuous oxygen therapy, but not in those on nocturnal oxygen therapy. Although continuous oxygen therapy decreased hematocrit **values** and increased survival, there is no evidence that these results are related to one another. Pulmonary vascular resistance also showed a differential effect of treatment. However, the **data** suggest that although continuous oxygen therapy reduced both mortality and pulmonary vascular resistance, the two phenomena were not related.

*Nocturnal Oxygen Therapy Trial Group: Continuous or Nocturnal Oxygen Therapy in Hypoxemic Chronic Obstructive Lung Disease: 4 **Clinical Trial**. Ann. Intern. Med. 93:391-398, 1980.

EXTRACORPOREAL SUPPORT FOR RESPIRATORY INSUFFICIENCY (ECMO)

Objective

To evaluate indications for the use and efficacy of extracorporeal membrane oxygenators (ECMO'S) for the support of patients with potentially reversible acute respiratory failure.

Summary Data

Mechanism:	Contract (Institute Initiated Clinical Trial)	
Initiation:	June 1974	
Total Duration:	3 years	
Funding:		
Total Support Prior to FY 1981	\$5,552,340	
FY 1981 Support	0	
Support Projected Beyond FY 1981		
Total Support	\$5,552,340	

Subjects

Males and females, ages 12 to 65, not stratified as to ethnic group, who had potentially reversible acute respiratory failure.

Experimental Design

Randomized, non-blind, fixed sample; 90 eligible patients were randomly assigned to a group receiving extracorporeal membrane oxygenation plus conventional therapy or to a group receiving conventional therapy.

Current Phase (As of October 1981): Concluded

Background

The report of the Task Force on Respiratory Diseases identified a clinical syndrome of acute respiratory insufficiency (ARI) and estimated that approximately 60,000 Americans die of ARI yearly. ARI **was** not precisely defined; indeed, the Task Force realized that pathologists do not recognize ARI. The Task Force pointed out that no diagnostic tests for early detection of ARI exist, that the incidence and prevalence of the disease are not known, and that existing therapy is supportive and nonspecific (diuretics, corticosteroids, etc.). The pathogenesis of the syndrome, the mechanism of interstitial edema, the defenses of the lung against agents causing ARI, and the ultrastructural pathology and natural history of the disease were virtually unknown. The Task Force indicated a need for Respiratory Care Centers with highly trained personnel that could reduce mortality from ARI.

This clinical trial grew out of the Task *Force* report. Nine participating centers defined ARI in clinical and physiological terms and agreed to a prospective randomized control study for 3 years to compare treatment of severe ARI by conventional means with treatment by extracorporeal membrane oxygenators.

Extracorporeal **support** for Respiratory Insufficiency (ECMO)

Animal studies have shown that ECMO'S can provide one to two **Weeks'** support for the lungs without serious blood damage, in contrast to bubble oxygenators, which allow complete pulmonary bypass for approximately 6 hours, after which severe blood damage occurs at the direct blood-gas interface. If patients with hypoxia secondary to acute reversible lung injury can be supported with ECMO'S until the lung lesion heals, improvement in survival rates and avoidance of the hazards of conventional therapy may result. The trial, now completed, was conducted at nine clinical centers in the United States.

Trial Results

Among the 90 patients in the randomized study, mortality for all groups was over 90 percent, and there were an equal number of survivors in the group receiving conventional therapy alone and in the group receiving extracorporeal membrane oxygenation plus conventional therapy. Morphological studies of biopsy and autopsy material from the study group support the view that, despite sophisticated technology, the progression of lung disease in patients with severe acute respiratory failure cannot be arrested by the use of ECMO.

GRANULOCYTE TRANSFUSION STUDY

Objective

To evaluate granulocyte transfusion therapy with respect to its prophylactic and therapeutic effectiveness to prevent and aid recovery from infection. The study trials were conducted simultaneously.

Summary Data

Mechanism:	Contract (Institute Initiated Clinical Trial)	
Initiation:	September 1976	
Total Duration:	4 years	
Funding:		
Total Support Prior to FY 1981	\$1,635,142	
FY 1981 support		0
Support Projected Beyond FY 1981		0
Total Support	\$1,635,142	

Subjects

Prophylactic Trial: **males and females, 12 years or older, who were in the first induction phase of chemotherapy for acute leukemia, who had severe neutropenia, and who did **not have** documented infection.**

Therapeutic Trial: **males and females, any age who were receiving chemotherapy for acute leukemia *or* who may have had aplastic anemia, who had severe neutropenia, and who had documented infection.**

Experimental Design

Prophylactic Trial and Therapeutic Trial: randomized, non-blind, sequential. eligible patients were randomized to daily granulocyte transfusions or no granulocyte transfusions.

Current Phase (As of October 1981): Analysis and Dissemination

Background

Infection remains a major cause of death in patients receiving chemotherapy for malignant diseases. One approach to the problem of septicemia and high mortality in these patients is the therapeutic use of granulocyte transfusions. Recent improvements in collection techniques, employing continuous flow centrifugation, **now** permit the collection of granulocytes from a single, **normal** donor in sufficient numbers to study their application in the treatment of infections in granulocytopenic patients. Recent studies have demonstrated the efficacy of granulocyte transfusions as an adjunct in the therapy of septicemia due to gram negative microorganisms associated with granulocytopenia.

The **aims** of the study were to determine (1) whether infections can be prevented in patients who receive granulocytes prophylactically and (2) whether recovery from infection is aided in patients who receive granulocytes therapeutically. Both trials utilized controls who received no granulocytes.

Granulocyte Transfusion Study

Four contracts were awarded in September 1976. The protocol designed to evaluate the efficacy of prophylactic granulocyte transfusions was completed at the close of 1977. The protocol for the therapeutic trial was completed in April 1978. 102 patients were randomized in the Prophylactic trial and 51 in the therapeutic trial. The Recruitment and Intervention Phase ended in February 1980. The trial is now in the Analysis and Dissemination Phase.

Trial Results (Prophylactic Transfusion Study)

54 patients were randomized to receive daily granulocyte transfusions and 48 were randomized to the control group. Granulocyte transfusions were given for 28 days. The primary end-point was the occurrence of documented infection during the study period. Patients were monitored and data collected daily. Additional evaluations were performed 35 and 60 days after randomization and at six month intervals thereafter. The incidence of bacterial septicemia was significantly lower in patients given transfusions (9 per cent) than in controls (27 percent). The incidence of pneumonia was twice that in transfused patients than in controls. Granulocyte transfusion did not reduce the incidence of other infections or improve bone-marrow recovery, remission rate and duration, or survival. Seventy-two percent of the patients given transfusions had transfusion reactions and fifty-seven percent had pulmonary infiltrates versus twenty-seven percent of the controls. Thirty-five percent of the patients with pulmonary infiltrates died versus five percent of those without infiltrates. It was concluded that prophylactic granulocyte transfusions should not be used during remission-induction chemotherapy in acute myelogenous leukemia because the risks outweigh the benefits.

COOPERATIVE STUDY OF FACTOR VIII INHIBITORS

Objective

To test the efficacy of prothrombin complex concentrates (Factor IX) in the treatment of hemophiliac patients who have inhibitors to Factor VIII.

Summary Data

Mechanism:	Contract (Institute Initiated Clinical Trial)
Initiation:	July 1978
Total Duration:	2 years (Intervention: 1 year)
Funding:	
Total Support Prior to FY 1981	\$782,350
FY 1981 Support	0
Support Projected Beyond FY 1981	0
Total Support	\$782,350

Subjects

Males, not stratified as to ethnic group, who had hemophilia.

Experimental Design

Double-blind study; patients *served as* their own controls. A total of 51 patients. Each patient received a single large dose of Konyne, Proplex, or diluted albumin (as a control). Joint bleeding of the elbow, knee, and ankle were evaluated 6 hours after each dose.

Current Phase (As of October 1981): Concluded

Background

Despite major advances in the treatment of patients with hemophilia, a serious remaining challenge is presented by the occurrence of circulating inhibitors to Factor VIII. Because of lack of information on the natural course of patients with Factor VIII inhibitors, the relative efficacy of various modes of therapy is not established. The Division of Blood Diseases and Resources decided to sponsor a clinical investigation which would evaluate populations of hemophilia patients for Factor VIII inhibitors, follow up these patients to provide information on the natural history of the inhibitor in the hemophilia patients, and make available a reference center to monitor results and attain uniformity.

cooperative -Study "

Factor VIII Inhibitors

Treatment of a patient with a severe inhibitor and consequent bleeding remains a problem. Management includes protracted treatment with Factor VIII, use of immunosuppressive agents, and most recently, the use of prothrombin complex (or Factor IX) concentrates. The rationale for Factor IX is that it bypasses the defect in Factor VIII caused by the inhibitor. This method of therapy has attracted wide popularity, but the success is greatly debated. It was intended at the very outset of the Factor VIII study that therapeutic trials involving patients with inhibitors would not be a prime function, but that such studies would be monitored if necessary. A control trial of Factor IX concentrates therapy was strongly advised by the DBDR Advisory Committee. Accordingly, during fiscal year 1978, a protocol for a double-blind control study was developed by the Factor VIII inhibitor group. The trial began in the spring of 1978, and the intervention concluded about 1 year later. The trial has been concluded.

Trial Results

Results were published in August 1980 indicating that although Factor IX, when used in a single dose, is only partially effective in the treatment of joint hemorrhage in hemophiliacs with inhibitors, its continued use for acute hemarthrosis is justified in the absence of any other effective and readily available therapy for this disorder.*

*Lusner, JM, Shapiro, SS, Palascak, JE, et al.: Efficacy of Prothrombin-Complex Concentrates in Hemophiliacs with Antibodies To Factor VIII. N Engl J. Med. 1980; 303:421-425.

MANAGEMENT OF PATENT DUCTUS IN PREMATURE INFANTS

Objective

To evaluate the effects (up to one year of age) of indomethacin on the clinical course of patent ductus arteriosus in premature infants (24 hours old or less) and to assess the relative merits of indomethacin and surgery in infants with persistent respiratory distress who were not treated early with indomethacin. Two concurrent trials are to be performed.

Summary Data

Mechanism:	Grant (Investigator Initiated Clinical Trial)
Initiation:	September 1978
Total Duration:	4 years (Intervention and Follow-up: 2 years)
Funding:	
Total Support Prior to FY 1981	\$3,543,332
FY 1981 Support	576,763
Support Projected Beyond FY 1981	0
Total Support	<u>\$4,120,095</u>

Subjects

Premature infants with patent ductus arteriosus, males and females, with birth weights of 1,750 gm or less, admitted to the participating institutions within the first 24 hours of life. Total sample size was 400 for Trial A and 140 for Trial B.

Experimental Design

Trial A was a randomized, double-blind trial in which indomethacin plus usual medical therapy was compared with a placebo plus medical therapy. Where this regimen was unsuccessful, the code was broken, and infants who received Indomethacin were treated surgically. Infants who had received placebo in Trial A were entered, if there are no contraindications to indomethacin, into Trial B. In Trial B, infants were randomized to immediate surgery or indomethacin therapy. Those in whom indomethacin treatment is unsuccessful were be treated surgically.

Current Phase (As of October 1981): Intervention (Follow-up)

Background

The incidence of patent ductus arteriosus is higher in premature infants than in full-term infants and is highest in premature infants who have respiratory distress syndrome. It is generally agreed that intervention in an asymptomatic infant with a small left-to-right shunt is unnecessary, since the patent ductus almost invariably closes spontaneously and thus does not require surgery. A few infants will demonstrate signs of a large shunt during the course of respiratory

Management of Patent Ductus in Premature Infants

distress syndrome. Many of these infants will improve with medical management of congestive heart failure, but others require surgical closure. A third group of babies with respiratory distress have severe progressive pulmonary disease requiring ventilator support. There is disagreement as to whether elimination of the patent ductus in these infants results in decreased mortality. A variety of therapeutic approaches is being used, and there is no convincing evidence of the superiority of one treatment over another.

The Recruitment and Intervention Phase began in April 1979. Recruitment was completed March 31, 1981 with the recruitment goal of 400 patients met.

Preliminary Trial Results

At the time of hospital discharge, mortality and morbidity was very similar in the early indomethacin group, the delayed indomethacin group, and the usual medical therapy plus surgery group. However, in the two groups who received indomethacin, surgery was necessary to close the ductus **in only 30% of cases, as opposed to 70% in the group** who did not receive indomethacin. Thus, it appears that the use of indomethacin eliminates the need for surgery in 40% of the infants with this condition. All patients will be followed for one year after hospital discharge, with these results to be released in 1982.

Hepatitis B VACCINE CLINICAL TRIAL

Objective

To determine the efficacy of a new vaccine to prevent hepatitis B.

Summary Data

Mechanism: Grant (Investigator Initiated Clinical Trial)
 Initiation: November 1978
 Total Duration: 3 years (2 years Intervention and Follow-Up)
 Funding:

Total Support Prior to FY 1981	\$100,000	estimated
FY 1981 Support	100,000	"
Support Projected Beyond 1981	0	lt
	200000 -t	

Subjects

Males at high risk for hepatitis B virus infection, 36 years of age or younger, no recent symptoms of hepatitis, blood specimen negative for HBsAg, anti-HB_s and anti-HB_e.

Experimental Design

Randomized, double blind, fixed-sample. Total sample size was 1083. 549 subjects were allocated to the vaccine group in which they were treated with highly purified formalin-inactivated virus subunits derived from the plasma of chronic carriers of hepatitis B. 534 were allocated to the placebo group. Both groups received injections at 0, 1 month, and 6 months unless evidence of infection developed before the series was completed.

Current Phase (As of October 1981): Concluded

Background

Although most carriers of HBsAg are asymptomatic, a substantial proportion eventually develop chronic active hepatitis and cirrhosis. There is also overwhelming evidence that the hepatitis B virus is the single most important causative factor of hepatocellular carcinoma. Thus, mass immunization programs against HBV infection may ultimately affect not only the incidence of acute hepatitis B and the pool of chronic carriers but may also reduce the morbidity and mortality from chronic active hepatitis, cirrhosis, and hepatocellular carcinoma.

Krugman and his co-workers laid the groundwork for active immunization against hepatitis B in 1970 to 1973. They discovered that a 1:10 dilution of hepatitis B infective serum lost its infectivity when boiled for one minute but retained its antigenicity and prevented hepatitis B in 70% of vaccinated subjects. Hilleman and his colleagues at the Merck Institute of Therapeutic Research developed a more sophisticated vaccine consisting of highly

Hepatitis B Vaccine Clinical Trial

purified, formal in-inactivated HB_sA_g particles derived from the plasma of chronic carriers of the antigen. By 1970, data were sufficient to permit testing in a clinical trial.

The first subject was inoculated in November 1978, and by December 1979, recruitment had ended. In May 1980, all trial events were reviewed and classified by an expert panel. In June 1980 the code of vaccine and placebo allocation was broken.

Trial Results

Within one month of the first vaccination, 31.4 percent of persons receiving the vaccine developed antibody against hepatitis B; within two months, this rate increased to 77 Percent; within three months, to 87 percent; and within six months, but before the third injection, to 90 percent. The booster injection increased the antibody-response rate to 96 percent. Antibody-response rates then remained essentially unchanged for the rest of the 18-month followup period. The incidence of chemical or serologic evidence of hepatitis B in vaccine recipients varied between 1.4 percent and 7.6 percent compared with 18.1 percent and 35.0 percent in placebo recipients.

III: Recently Initiated Trials (FY 1981)

A RANDOMIZED TRIAL OF ASPIRIN AND MORTALITY IN PHYSICIANS

Objective

To assess the effect on cardiovascular mortality of alternate-day consumption of 325 milligrams of aspirin and, secondarily, the effect on cancer incidence of alternate-day consumption of 30 milligrams of beta-carotene.

Summary Data

Mechanism: Grant (Investigator Initiated Clinical Trial)

Initiation: September 1981

Total Duration: 5 years (Intervention 4.5 years)

Funding:

Total Support Prior to FY 1981	\$	
FY 1981 Support		505,00: *
Support Projected Beyond FY 1981		<u>1,866,153</u>
Total Support		\$2,372,155

Subjects

Male physicians, age 50 to 75, who report no history of stroke, myocardial infarction, cancer, or renal disease, who indicate no contraindications to aspirin or beta-carotene and who report no current usage of aspirin or Vitamin A tablets greater than once per week. Sample size is estimated to be 21,900.

Experimental Design

Randomized, double-blind, fixed sample. Participants are to be randomized into one of four treatment groups: one 325 milligram aspirin tablet every other day, alternating with one 30 milligram capsule of **beta-carotene**; one aspirin every other day, alternating with one capsule of beta-carotene; and one aspirin Placebo tablet every other day, alternating with one capsule of beta-carotene placebo. Major endpoints for the cardiovascular component of the study are cardiovascular mortality, total mortality, and coronary events.

Current Phase (As of October 1981): Planning

Thrombosis plays a major role in the late stages of coronary occlusion. Platelet aggregation is a large component in the formation of arterial thrombi. In pharmacologic studies, aspirin has been shown to inhibit platelet aggregability and, therefore, might be expected to prevent coronary occlusion. These effects are apparent in the dose range of 100-1000 mg/day, and may be most evident at 160 milligrams daily. Higher doses seen to be no more effective in either inhibition of platelet aggregability or prolonged bleeding time.

*Joint funding by NHLBI and NCI. Total dollars spent in FY 1981 were \$843,336. NHLBI financed \$506,002 and NCI \$337,334. Total dollars, including estimated indirect costs, committed through FY 1985 are \$3,110,254, of which NHLBI is to fund \$1,866,153 and NCI to fund \$1,224,101.

PRIMARY PREVENTION OF Hypertension (FEASIBILITY STUDY)

Objective

To determine whether hypertension can be prevented by dietary interventions in a population of 19-40 year old high risk men and women.

Summary Data

Mechanism: Grant (Investigator Initiated Clinical Trial)

Initiation: September 1981

Total Duration: 5 years (Feasibility Study)

Funding:

Total Support Prior to FY 1981	\$
FY 1981 Support	1,121,387
Support project Beyond FY 1981	9,811,873
Total Support	<u>\$10,933,260</u>

Subjects

Males and females, ages 18-40, first degree relatives of hypertensive patients in the HDFP study, first degree relatives of clinic hypertension patients, and patients identified through screening. Patients will have initial home diastolic blood pressure between 78-96 mm Hg, subsequent clinic readings between 80-89 mm HG and Quetelet body mass index of more than 0.035 and less than 0.061. 800 patients will be required.

Experimental Design

Randomized, non-blind, with five groups of 160 patients each. The groups include: a control group with no intervention; a low sodium group with a goal of 70 milliequivalents sodium intake per day; a low sodium, high potassium group with a goal of 70 milliequivalents sodium and 100 milliequivalents potassium per day; a weight reduction group with a goal of more **than five percent** reduction in body weight; and a body weight reduction and low sodium intake group.

Current Phase (As of October 1981): Planning

Background

Animal studies conducted over recent decades have shown that excess dietary sodium chloride induces hypertension in a large fraction of most mammalian species and that excess dietary potassium chloride protects against the hypertensogenic action of excess sodium chloride. Human population groups which consume less than three grams of sodium chloride per day do not show the rise in blood pressure with increasing age that occurs in populations in industrial nations. A variety of studies have shown the relationship of body mass to blood pressure, leading many investigators to believe excess weight to be the leading risk factor for high blood pressure. Intervention trials have demonstrated that weight reduction in the absence of substantial change in sodium excretion results in reducing blood pressure in hypertensive. The study is in the Planning Phase, in which the protocol will be refined and the manual of operations developed. Included in the study are four clinical centers, a coordinating center, and a nutrition and education resource center.

IV: Trials in the Planning Stage

ANTIARRHYTHMIC AGENTS IN THE PREVENTION OF SUDDEN DEATH: PILOT STUDY

Objective

To conduct a pilot study in order to compare the effectiveness of various drugs and drug combinations in suppressing ventricular arrhythmias, and to evaluate their safety. This pilot study will also assess the feasibility of carrying out a full scale clinical trial. The objective of the full trial, if it is conducted, will be to determine if the suppression of ventricular arrhythmias in people with coronary heart disease will result in reduction in sudden cardiac death.

Proposed:

Mechanism: Contract (Institute Initiated Clinical Trial)

Initiation: September 1982

Total Duration: 4 years (Pilot Study)

Funding:

Total Support \$8,000,000

Subjects

Patients in the post-MI period who have major ventricular arrhythmias.

Experimental Design

About 500 patients would be enrolled and randomized to five groups. About 100 patients per group is required in order to obtain reliable information on toxicity and to analyze results by subgroups.

The drugs studied will be chosen from among amiodarone, aprindine, disopyramide, encainide, flecainide, lorcinide, mexiletine, procainamide, quinidine, and tocainide. Each group will follow a pre-determined treatment strategy. Initially, patients will be prescribed one of five drugs. After a three month interval, efficacy in decreasing ventricular arrhythmias will be assessed. Then, depending on the degree of arrhythmia suppression and occurrence of side effects, a second drug will supplement or replace the first drug.

Background

Approximately 400,000 people in the U.S. die suddenly every year, most of them presumably from cardiac arrhythmias. Three quarters of this population has known heart disease. Epidemiologic studies have indicated that complex ventricular premature beats make an independent contribution to risk of sudden death in survivors of myocardial infarction and do not appear to be *merely* a reflection of their association with

Antiarrhythmic Agents in the Preventing of Sudden Death: Pilot Study

relatively severe myocardial damage. The potential for reduction in mortality by identification and administration of drugs capable of safely suppressing ventricular arrhythmias is tremendous. Currently, there is incomplete knowledge regarding which types of ventricular arrhythmias respond to various kinds of drugs. This pilot study of antiarrhythmic agents would help clarify this issue.

ISOLATED SYSTOLIC HYPERTENSION IN THE ELDERLY

Objective

To determine the effect of treating isolated systolic hypertension (ISH) in persons over 60 years of age.

Proposed

Mechanism: Contract (Institute Initiated Clinical Trial)

Total Duration: 7 years (Intervention 3 years)

Funding:

Total support \$70,000,000

Subjects

Males and females, over 60 years of age and with systolic blood pressure greater or equal to 160 mm Hg and a diastolic blood pressure **less than 90** mm Hg. Total sample size is 4,000.

Experimental Design

Randomized, double blind, placebo controlled. All patients would be treated and followed for three years, the primary endpoint being the occurrence of stroke, or other cardiovascular events.

Background

The classical form of essential hypertension is a relative increase in both the systolic and the diastolic components of the blood pressure. Attention so far has primarily focused on elevated diastolic pressure and it has been shown, beyond doubt, that effective treatment of this condition **results** in not only reduced mortality, but also in a lesser risk of subsequent cardiovascular and renal complications. The prevalence of combined systolic-diastolic hypertension tends to stabilize in late middle age. However, with increasing years the systolic pressure continues to rise out of proportion to any concomitant rise in the diastolic component. Hence the emergence in the elderly population of the condition known as isolated systolic hypertension (ISH).

It was once believed that the complication of hypertension could be completely accounted for by the diastolic elevation alone. There is now abundant evidence that the systolic component is at least as equally predictive of future morbidity and mortality. Therefore effective treatment of **ISH** in the elderly population might reduce premature mortality and the occurrence of disabling cerebrovascular, cardiovascular and renal disease. ISH may also play an important part in the etiology of senile dementia.

To determine whether a large study is now feasible the National Heart, Lung, and Blood Institute is sponsoring, in conjunction with the National Institute on Aging, a pilot study of systolic hypertension in the elderly. This will recruit a total of 500 patients from five centers and treat and follow them all for at least one year. This small pilot has specific objectives **each** designed to test and evaluate critical components of a future full-scale endeavor directed at the consequences of treating **ISH** in the elderly.

STREPTOKINASE IN THE TREATMENT OF MYOCARDIAL INFARCTION

The use of intracoronary or intravenous streptokinase in the treatment of acute myocardial infarction is showing dramatic effects upon relieving acute coronary obstruction. This trial will assess the effectiveness of streptokinase under controlled clinical procedures in order to prevent inappropriate widespread clinical use without inadequate validation of net benefit. Details of this trial are under development.

EVALUATION OF VENTILATION-PERFUSION SCANS AND PULMONARY ANGIOGRAPHY FOR DIAGNOSIS OF PULMONARY EMBOLISM

Objective

To **evaluate** the effectiveness of ventilation-perfusion scans as a less dangerous and less costly alternative and adjunct technique to pulmonary angiography, for the diagnosis of pulmonary embolism. The outcome is expected to solve a major medical controversy with important implications for reducing the risks associated with the diagnosis and treatment of pulmonary embolism.

Proposed

Mechanism: Contract (Institute Initiated Clinical Trial)

Total Duration: 4 years (Recruitment 2 years)

Funding:

Total Support \$70,000,000

Subjects

Patients suspected of having pulmonary embolism. Total sample size is 700.

Experimental Design

Non-randomized, non-blind, fixed sample. The trial would involve 700 patients who would receive ventilation perfusion scans; negative scans would result in detailed followup; equivocal and positive scans would lead to pulmonary angiography for definitive diagnosis and followup.

Background

Pulmonary embolism refers to a blood clot blocking one or more arteries in the lung. The problem is associated with patients recovering from major surgery, patients with poor circulation, childbirth, women taking oral contraceptives, and patients with underlying cancer. **In the last decade despite diagnostic advances the condition remains difficult to diagnose.** Postmortem exams have shown a high incidence of undiagnosed pulmonary emboli, conditions that in many cases may have been associated with the patient's death. Recent estimates indicate that pulmonary embolism may account for 50,000 deaths each year. **If less than one embolic event in 10 is fatal, there are an estimated half a million episodes of pulmonary embolism each year in hospitalized patients in the United States.**

The primary immediate hospital treatment for pulmonary embolism, anticoagulation therapy with heparin is dangerous, **being the leading cause** of adverse drug reactions **in** hospitalized patients. Moreover, the followup treatment with the oral anticoagulant coumadin represents some risk since that drug is one of the eight drugs most commonly responsible for hospital admission.

This trial will assess the accuracy of ventilation-perfusion scans, a radio-nuclide imaging technique, **in** diagnosing pulmonary embolism, comparing **this technique** to the more invasive and more dangerous, standard technique of pulmonary angiography.

SLOW CHANNEL CALCIUM BLOCKER IN PATIENTS WITH CORONARY ARTERY SPASM

Objective

To evaluate the efficacy of a slow channel calcium blocker in patients with coronary artery spasm.

Proposed

Mechanism: Contract (Institute Initiated Clinical Trial)

Total Duration: 6 years (Recruitment 2 years)

Funding:

Total Support \$8,000,000

Subjects

Patients with coronary artery spasm. These patients would be identified primarily on the basis of angina at rest. However, a number of patients with chronic stable angina and acute myocardial infarction may also be shown to have coronary artery spasm and would be eligible for the study. The primary endpoint would be death plus nonfatal myocardial infarction. Reduction in angina would also be measured. Total sample size is 650.

Experimental Design

Double blind, multicenter, controlled trial.

Background

In recent years, there has been a resurgence of the concept that coronary artery **spasm** plays a major role in cardiac disease. The major area is thought to be unstable angina. However, there is some evidence that some people with chronic stable angina also have coronary artery spasm. In addition, studies have shown that of those with acute myocardial infarction, perhaps 5% have no evidence of vessel disease and 25% have evidence of only one vessel disease. Coronary artery spasm may play a role there as well.

Slow channel blockers (calcium antagonists) have received recent attention in the relief of the symptoms of coronary artery spasm. A number of small or uncontrolled studies have been done in patients with spasm and have shown promising results in relief of variant angina and ventricular arrhythmias (which often accompany variant angina). However, a large controlled study is needed to demonstrate whether these agents are indeed beneficial in reducing mortality and morbidity.

Previous studies have demonstrated the feasibility of identifying eligible patients and extended treatment with acceptable compliance and toxicity levels. A trial with about 10 centers is necessary to recruit the 650 patients necessary for a two-arm study. Recruitment would take two years, with one additional year of follow-up.

PHYSICAL EXERCISE IN SURVIVORS OF MYOCARDIAL INFARCTION

Objective:

To test the effect of physical exercise in survivors of myocardial infarction.

Proposed

Mechanism: Contract (Institute Initiated clinical Trial)

Total Duration: 7 years (Recruitment 2 years)

Funding:

Total Support \$50,000,000

Subjects

Post-myocardial infarction patients.

Experimental Design

Randomized, controlled trial. Four thousand subjects would be allocated either to Special Intervention, comprising an individually designed training program and risk factor counseling, or to usual Care from their primary physicians.

Background

One third of all deaths in the United States are the direct result of coronary heart disease (CHD), making it the leading cause of death. The patient who survives an MI has not only an increased chance of dying but also risks significant morbidity from cardiovascular and renal complications. Myocardial infarction often comes at a time when a subject has significant responsibilities both at home and at work.

Of the approximately one million persons suffering their first coronary event each year, roughly 400,000 of them die in the acute phase. The 600,900 who survive face a 10% chance of dying in the first year after the event, resulting in an additional 50,000 deaths. Therefore a reduction of even twenty percent would result in a substantial saving of lives. In five exercise trials to date, while none demonstrated a significant reduction in mortality (perhaps because of inadequate sample size), all had a positive trend favoring the exercise group ranging from 18.8% to 37.0%. Any new trial undertaken in this area would need to be sufficiently large to permit a true beneficial effect on mortality to be detected. To date, exercise appears to be one of the most promising interventions in a post-MI population. Increasing interest in this field by practicing physicians and the general population would most likely encourage participation in a post-MI clinical trial of physical exercise.

PREVENTION OF SUDDEN DEATH IN SURVIVORS
OF OUT-OF-HOSPITAL VENTRICULAR FIBRILLATION

Objective

To evaluate an antiarrhythmic agent in patients who recover from out-of-hospital ventricular fibrillation.

Proposed

Mechanism: Contract (Institute Initiated Clinical Trial)

Total Duration: 5 years (Recruitment 2 years)

Funding:

Total Support \$5,000,000

Subjects

Patients who have recovered from out-of-hospital ventricular fibrillation. Total size is 400.

Experimental Design

Randomized, multicenter trial.

Background

The number of community programs aimed at reducing heart disease mortality in the pre-hospital phase is increasing. The greater sophistication of ambulance and other rescue services plus the spread of cardiopulmonary resuscitation programs are likely to result in many more survivors of ventricular fibrillation. Recurrence of fibrillation is extremely likely in this population, especially in those without a demonstrable myocardial infarction accompanying the fibrillatory episode. In fact, there is often an absence of any other identifiable cardiac pathology. Therefore, if the ventricular fibrillation could be prevented, a major increase in life span might be expected. Currently, there is no accepted therapy which will prevent recurrence of fibrillation. At the same time, there are a number of promising, new antiarrhythmic drugs. Therefore, the time is appropriate to assess one or more of these drugs.