with well-defined pituitary tumors achieved remis­
sion of their disease, whereas the one patient who
apparently did not have a pituitary tumor did not
respond to the procedure. It seems reasonable to
suggest cryosurgery might be excellent treatment
for the patient who has demonstrable sarcoen
enlargement or hyperpigmentation when the diagnosis
of Cushing's syndrome is first made. Unfortunately,
these symptoms do not ordinarily occur until
after bilateral adrenalectomy (eg, patient 8). A

A most important feature of the experience thus far
is the relatively low morbidity of the pro­
cedure. With the exception of patient 6, none of
the patients developed rhinorrhea, meningitis, cranial nerve injuries or other central nervous system dam­
age, or significant diabetes insipidus. Patient 6 differed from the others with respect to surgical
technique in deeper penetration and a greater num­
er of lesions being utilized to achieve complete
obliteration of the tumor. Recovery of the pituitary region through the stereo­
diagnostic guide was easily performed and was of great
value. This was done without morbidity in a num­er of other patients, not reported here, for diag­
nostic purposes and to detect cystic lesions.

It is our impression that stereotaxic cryosur­
gery is quite advantageous, particularly in those
situations where more radical therapy is undesir­
able and perhaps unwarranted by a borderline
clinical situation. The technique may offer a use­
ful compromise between craniotomy and conven­
tional, relatively ineffective pituitary irradiation.
It is also conceivable that improvement of pituitary
function may be achieved in some patients with
pituitary tumors subjected to cryoablation. This
rarely occurs with other methods of treatment.

Don T. Nelson, MD, provided data regarding patients 1 and 5.
Soleiman A. Beres, MD, and Rosiny S. Yalow, MD, evaluated the growth hormone assays during the early phase of this study.

This investigation was supported in part by Public Health Service grant CA-04623.

Generic and Trade Names of Drug

Densametastase-Debrocan, Densal, Gancercinocut, Hender. Denmark.

References


Effect of the Anti-Coronary Club Program on Coronary Heart Disease Risk-Factor Status

George Christakis, MD, Seymour H. Rinaldi, MD, Morton Archer, MRA, MPH, and Arthur Kraus, ScD

A group of 814 men at large, 40 to 59 years old, have been placed in a diet relatively rich in polyunsaturated fatty acids. The study diet has significantly lowered the serum cholesterol levels and maintained these lower levels for periods as long as five years. The study proto­

col has also been effective in significantly reducing the incidence of obesity and hypertension during the first four years of study participation. Among a control group of 463 men of similar age, the prevalence of these con­
ditions was stable. After the men had participated in the study for four years, the differences between the experi­
mental and control groups in prevalence of these risk
factors (obesity, hypertension, and hypercholesterolemia) were statistically significant. Accompanying these signifi­
cant differences, a statistically significant difference
was observed between the two groups in morbidity for new coronary heart disease.

The Anti-Coronary Club Study* tests the hy­
pothesis that adherence to a serum cholesterol­
lowering diet will be associated with a decreased incidence of coronary heart disease. This project
was conducted by the Bureau of Nutrition of the New York City Department of Health since 1957. In previous reports the composition of the experimental diet (the "prudent diet") has been described, and data have been presented which suggest that adherence to this diet signifi­
cantly lowers the level of serum cholesterol of
both normal and overweight subjects with or with­out coronary disease. The remaining 277 subjects have been ex­
cluded from this report because of a history of clinical or electrocardiographic evidence of coro­

nary heart disease on entry to the study.

Method

Experimental Group.—Since the inception of the Anti-Coronary Club Study in June 1957, 1,091
male volunteers aged 40 to 69 years enlisted. The
volunteers responded initially to a radio and press
call for study participants. Subsequent volunteers were
drawn largely from referrals made by the original Anti-Coronary Club members. This report
considers the 814 subjects of this total who were
free of prior evidence of clinical coronary heart
disease. The remaining 277 subjects have been ex­
cluded from this report because of a history of clinical or electrocardiographic evidence of coro­

nary heart disease on entry to the study.

Table 1 shows that as of Dec 31, 1963, the end of the observation period, regarding the occurrence
of new coronary disease events for this report, 814 men had accumulated 2,357 person-years of
experience while in an active status. Active status
denotes regular attendance approximately every
five weeks for venipuncture and serum cholesterol
determinations and consultation with a nutrition­
list; every ten weeks for a clinical and nutrition
review session by a panel of physicians; and a
yearly involved medical history, with physical, laboratory, electrocardiographic, and roentgenographic
exami­nations.

* JAMA, Nov 7, 1966 • Vol 198, No 6

Generic and Trade Names of Drug

19. JAMA, Nov 7, 1966 • Vol 198, No 6

TRAGEDY MARKS DISCOVERY OF ANESTHESIA—
Failure to publicize his discovery, used as a general anesthesia almost cost Crawford W. Long (1815-1878) the honor of being the first to use ether for that purpose. After considerable controversy, it has now become clear that the fact that the honor goes to him. He used the drug for the removal

Long received his MD degree from the University of Pennsylvania in 1839 and returned to his native state of Georgia to practice. His discovery, three years later, was not recorded in medical annals until others had reported similar experiments in tooth extraction in October 1846. Long's first article on the subject was published in December 1846. Tragedy marked the discovery of this great boon to mankind. Long died in ob­
scenity. His immediate successors (Wells, Morton, and Jackson) identified with the ease of use of ether in dentistry were involved in litigation. One became insane and com­
The validity of comparing coronary heart disease incidence in the experimental group consuming the study diet, and the control group maintaining its usual diet pattern, depends on the comparability of other factors such as demographic and risk factors associated with coronary heart disease as they exist in the two groups on entry. Accordingly, a detailed demographic analysis of the experimental and control groups was performed and described in a previous report.* This analysis indicates that the significant/100 mg of dietary cholesterol intake was that of an experimental or a control subject; he utilized data from the physical examination as an indication of normal cardiovascular examination and as an indication of normal cardiovascular examination. The 'Diagnostic Criteria.'—The classification of new events representing myocardial infarction was that of the Cooperative Control of the American Heart Association, which included the following categories: (1) myocardial infarction, definite; (2) myocardial infarction, definite by ECG alone; (3) coronary thrombosis, definite; (4) coronary sclerosis, definite by autopsy; (5) ECG abnormalities, non-concordant with coronary artery disease; (6) angina pectoris, definite, with ECG changes; (7) angina pectoris, definite, without ECG changes. The clinical and electrocardiographic criteria for new coronary events were based on those recommended by the New York Heart Association. The chief cardiologist of the project assigned the classification of "definite event" when in his judgment the findings described in the above categories were met. He utilized data from the physical examination of subjects, mail and phone follow-up of subjects and their associates, and records from the subjects' families, physicians, hospitalizations, and death certificates. The complete records on all such "definite" events were then submitted to another cardiologist whose sole function on the project was to review critical events and evaluate this cardiologist was not aware whether the record under review was that of an experimental or a control subject; however, he submitted a report for his review included in the analyses in this report consists of 463 subjects who showed no initial evidence of coronary heart disease, by the same criteria applied to the experimental group. The two groups were quite comparable regarding the proportion with initial obesity and hypertension. The two groups were quite comparable regarding the proportion with initial hypertension. However, the experimental group had higher proportions of initial obesity and hypertension than the control group. In the light of these findings, it would be expected that the experimental group would develop a higher frequency of coronary heart disease than the control group.

The Experimental Diet.—A basic principle of the study diet was to provide approximately equal quantities of the three macronutrients: saturated, polyunsaturated, and monounsaturated. Beef, milk, and poultry were limited to four meals per week; poultry and vegetables were limited to four meals per week; and a minimum of one ounce of vegetable oil per day. The P/S ratio, without consideration of technical qualifications, is substantially the amount of polyunsaturated fatty acids divided by the amount of saturated fatty acids per 100 ml of serum cholesterol of the 478 experimental subjects and 420 control subjects 40 to 59 years old as of Dec 31, 1963. In the experimental group, a highly significant drop of about 30 mg/100 ml was observed after one year in the study. Therefore the concentration of serum cholesterol leveled off at about 225 mg/100 ml to maintain the serum cholesterol level fell about 7 mg/100 ml during the first two years, but rose thereafter so that by the end of the fourth year, the latest for which data are available, the average level had returned to its initial concentration.

Figure 1 shows the trends in the average level of serum cholesterol of the 478 experimental subjects and 420 control subjects 40 to 59 years old still active in the Anticoronary Club coronary control groups as of Dec 31, 1963. In the experimental group, a highly significant drop of about 30 mg/100 ml from an average of 255 mg/100 ml was observed after one year in the study. The experimental and control groups in each age category. The overall age-adjusted incidence rate in the experimental versus the control group was tested and found to be statistically significant at a level of 0.01. Of the eight new coronary events occurring among active experimental subjects, seven occurred during the first two years and one during the third year. The increase in the adjusted incidence rate in the experimental versus the control group was tested and found to be statistically significant at a level of 0.01. Of the eight new coronary events occurring among active experimental subjects, seven occurred during the first two years and one during the third year. The increase in the adjusted incidence rate in the experimental versus the control group was tested and found to be statistically significant at a level of 0.01. Of the eight new coronary events occurring among active experimental subjects, seven occurred during the first two years and one during the third year. The increase in the adjusted incidence rate in the experimental versus the control group was tested and found to be statistically significant at a level of 0.01.
poring that eight new events in the experimental group involved six definite myocardial infarctions, one definite angina with ECG changes, and one definite angina without ECG changes, while 12 new events in the control group involved six definite myocardial infarctions, four cases of definite angina without ECG changes, and two cases of definite myocardial infarctions, four cases of definite angina without ECG changes. The relative incidence rate in the experimental group among those who were initially obese and then reduced may be compared with that for men who did not reduce as well as with the rate for those who entered at normal weight. Although the total number of new events is still small, the age-specific incidence rates among the initially obese and the initially normal weight in the experimental group are about the same.

Inactive Experimental Group.—As seen in Table 1, confirmed new coronary disease events have been detected among those in the experimental group who shifted to inactive status. The observed incidence, although age adjusted, for the group is 139 per 100,000 person-years of experience in the inactive group. The rate in the inactive 40-49 age group is similar to the rate for fully participating experimental subjects in the same age group, while the rate for the other age groups is between that for the active experimental subjects and that for the control subjects, but closer to that for control subjects.

It is difficult to interpret precisely the findings in the inactive experimental group, since it is not known to what extent this group may have followed the study diet. Moreover, the detection of new coronary disease events which have occurred may not have been equally complete in the experimental and control subjects. However, the incidence in the inactive experimental group is intermediate between that for the active experimental and control subjects. This suggests that the difference in incidence between the active experimental and control subjects may be due to the Anti-Coronary Club participation.

Dropouts.—Of the 814 subjects who entered the experimental group, 476 remained active until the end of the observation period and 290 shifted to inactive status, as previously defined. The other 46 subjects are dropouts; that is, after a period of active status (averaging 15 months), they discontinued all contact with the study. The health status of these 46 dropouts was determined in June 1964, by telephone contact with the subjects, and home visits. This process revealed that a death from coronary heart disease had occurred among four subjects four years after he had dropped out of the study following less than a year's participation. A nonfatal coronary heart disease event was also reported for another subject, which occurred four years after he dropped out following four months' participation in the study. Of the remaining 44 dropouts, 42 were found to be alive and reportedly free of new coronary events; only two remain with unknown follow-up status.

Since only two new coronary events among dropouts from the experimental group were revealed by this process and these occurred in individuals with less than a year's full participation in the study, the findings do not affect our interpretation of the significant difference in incidence between the active experimental and control subjects.

Deaths From Coronary Heart Disease.—Of the eight subjects with new coronary disease events in the fully participating experimental group, three died of coronary heart disease, one died of other causes, and the four were still alive at the end of the observation period. Of the seven detected cases with new events in the inactive experimental group, all were myocardial infarctions, five died of coronary heart disease and the other two were still alive at the end of the observation period. Since all case fatalities were due to coronary heart disease deaths and none of these cases were due to other causes, the observed mortality in this group is substantially the same as that observed initially.

Of the 12 cases with new coronary disease events in the control group, all were still alive at the end of the observation period. Of these, seven died of death unrelated to coronary heart disease; only one new event remained at subject death, and the other four were still alive at the end of the observation period. Of the seven detectable deaths, there were 689 per 100,000 person-years in the experimental group, and 463 per 100,000 in the control group. The difference between these two rates is slight and not statistically significant.

Any two of the eight subjects had multiple risk factors and the increased number of these risk factors for the experimental group during their period of participation in the study, of interest and importance to recognize the impact of multiple risk factors with respect to the reduction in coronary heart disease deaths. For the 332 subjects in the active experimental group, the total risk factor score was 132. For the subjects in the control group who participated in the study for four years or more, the risk factor status was compared at time of entry to the study, after two years, and after four years of participation.

Change in Risk Factor Status Resulting From Study Participation.—Since the incidence of coronary heart disease of the experimental subjects was significantly lower than that of the control group during their period of participation in the study, it is of interest and importance to recognize the impact of multiple risk factors with respect to the three risk factors considered in this study. For the 332 subjects in the active experimental group, the total risk factor score was 132. For the subjects in the control group who participated in the study for four years or more, the risk factor status was compared at time of entry to the study, after two years, and after four years of participation.

Table 2.—Percent of Risk Factors Among 332 Experimental and 329 Control Subjects at Entry and After Two and Four Years of Observation

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Experimental</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry</td>
<td>Year 2</td>
<td>Year 4</td>
</tr>
<tr>
<td>None</td>
<td>14.1</td>
<td>25.1</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>38.3</td>
<td>41.8</td>
</tr>
<tr>
<td>Obesity†</td>
<td>40.4</td>
<td>34.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10.9</td>
<td>11.5</td>
</tr>
<tr>
<td>None</td>
<td>50.1</td>
<td>50.2</td>
</tr>
<tr>
<td>Any one</td>
<td>12.2</td>
<td>17.9</td>
</tr>
<tr>
<td>Any two</td>
<td>5.1</td>
<td>9.3</td>
</tr>
<tr>
<td>All three</td>
<td>2.0</td>
<td>6.0</td>
</tr>
</tbody>
</table>

*Percent of subjects who had one or more risk factors present at entry and after two and four years of observation.
†Percent of subjects who had one or more risk factors present at entry and after two and four years of observation.

In the experimental group, the prevalence of these risk factors decreased substantially after two years and remained decreased after four years. The prevalence of hypercholesterolemia declines from about 43% to about 20%, that of hypertension from about 26% to about 11%, and that of obesity from 56% to 16%. It should be noted that the initial prevalence of these risk factors for the experimental group was higher in each instance. Figure 2 presents the distribution of the subjects in the experimental and control groups by the number of risk factors present for the same periods of observation. In the control group, the distributions of the number of risk factors present after two and four years of observation have remained substantially the same as that observed initially. By contrast, the proportion of the experimental group with one or more of the risk factors has been a significant reduction. In the subjects exhibiting a single risk factor, the most impressive changes are the decreased numbers of subjects with multiple risk factors. As of this writing, 17% had none; two and four years later, these proportions had changed to about 6% and 60%, respectively.

The factor of obesity is worthy of more detailed analysis since both hypercholesterolemia and hypertension may be related etiologically or pathologically with this condition. The prevalence of hypercholesterolemia and hypertension according to the presence of obesity on entry and after years of observation is examined in Table 3.

On entry to the study, 187 of 332 experimental subjects were obese (56.3%); while of the 329 control subjects, 149 (45.6%) were obese. Of the obese experimental group subjects, 41.7% were hypercholesterolemic and 25.1% hypertensive; in the control group, 46.9% were obese, 23.0% hypercholesterolemic, and 21.1% hypertensive. On entry to the study, after two years, and after four years of participation in the study, the prevalence of obesity among the 332 experimental subjects and the 329 control subjects by weight status is examined in Table 3.

After four years of participation in the study, 57 men (17.5%) of the experimental group were obese; 53 belonged to the 187 men initially obese while the remaining four had been initially of normal weight. All rights reserved. Copyright 1964 Anti-Coronary Club—Christakis et al. 133 JAMA, Nov 7, 1966 • Vol 198, No 6 132
By contrast, 145 men in the control group were obese after four years; 129 were derived from the group of 149 initially obese while 16 of the initial subjects with hypercholesterolemia was about the obese after four years; the proportion hypercholesterolemic group after four years was significantly lower initial or final weight status or change in weight lower than the proportion of obese men hypercholesterolic group after four years was significantly lower.

Among the experimental subjects after four years, the prevalence of hypercholesterolemia and hypertension in the obese and normal-weight subjects was about the same in the control group, and remained comparable during the period of the study.

In order to make these estimates of cigarette smoking current, a survey was conducted of all the subjects, showing that the prevalence of cigarette smoking among the experimental group was significantly lower than that in the control group at the similar period of observation, thus suggesting that the prevalence of smoking habits of all 478 active experimental and control subjects could easily be explained by chance variations.

The data presented indicate that the incidence of new coronary events among the initially normal subjects of the Anti-Coronary Club program was significantly lower than that among the control group, and also lower than incidence rates reported in studies of comparable age groups. It seems reasonable to attribute this difference primarily to the effects of the Anti-Coronary Club program with its major feature of supervised adherence to a prudent diet. The reasons for this conclusion are as follows:

1. The group of entrants into the experimental group had no initial predilection for reduced coronary heart disease in comparison with the control group.

2. Those remaining in the active experimental group appear to have adhered to the prudent diet, as judged by regular and frequent interviews with the Anti-Coronary Club the sanatoriums and by progressive increase in the linoleic acid component of their diet.

3. A substantial and statistically significant decrease in serum cholesterol levels occurred during the first year of active status in the experimental group, and remained virtually stabilized at this lower level throughout the next six years of follow-up. The numbers of the control group, by comparison, showed a significant change by the end of the study period.

4. There was a substantial and statistically significant decrease in the number of new coronary events in experimental group subjects between the first two years of participation and the period from 1958 to 1964, this decrease in full participation, despite their increasing age. By contrast, the rate increased with the passage of time in the control group.

5. The incidence rate in the control group is not high in comparison to the incidence rates of the other prominent prospective studies already cited, indicating that the difference between the control group rate and that of the experimental group is due to an unusually high rate in the control group.

Many important questions relevant to the effects of the Anti-Coronary Club program have not yet been finally answered. The number of new coronary events through the end of the observation period of this report is admittedly small; the follow-up of the experimental and control groups will continue. As additional data accumulates, the meaningful analysis will be possible on a number of questions. Among such questions are whether the relatively low incidence rate is maintained in the experimental group as participation continues, and whether the new coronary events which occur among long-term participants in the experimental program can be related to other characteristics.

The prospective Framingham study has concluded the association between increased morbidity of coronary heart disease and the presence of specific risk factors. Among these have been hypercholesterolemia, obesity, and hypertension. The identification of such risk factors constitutes a major advance in the effort to control the public health problem of coronary heart disease. It would therefore appear reasonable to attempt to control coronary heart disease morbidity and mortality by these methods.

A previous report has shown that the study diet effective in lowering the serum cholesterol levels in men and in maintaining lowered levels for periods of as long as five years. The present report indicates that the protocol of the study was effective in significantly reducing the incidence of obesity and hypertension among the subjects in the experimental group over their first four years participation in the study. The incidence of other coronary heart disease morbidity and mortality by these methods.

The American Medical Association has recognized the importance of reduced serum cholesterol in high risk groups and has also suggested the need to control the risk represented by excessive serum cholesterol. The American Heart Association has recommended emphasis on the prevention of diet that lowered serum cholesterol and has recommended that appropriate dietary changes for the public in general should be instituted. If the results of these studies are similar to the present, there is reason to hope that progress can be made in determining the public health problem.
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Diet on the Serum Cholesterol Levels of Middle-Aged Men,
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5. Evaluation of Serum Lipoprotein and Cholesterol Measure­

EMPLOYMENT OF CARDIAC PATIENT.—Most forward looking businesses today recog­
ize that good medical programs save waste and dissipation of assets just as surely as audi­
enes.1 It is the principal reason for the growth of industrial medical units that employers
try—from emergency service first aid stations to the well-equipped, expertly staffed organizations
better serve the needs of all members of an organization.

First: When new people are employed, careful physical examinations can help place those with

Second: Medical counseling has stepped up programs for periodic physical examinations of key
employees, to detect health problems at an early stage, an extremely important part of the control
of heart disease. At the same time these programs contribute to better mental health by alleviating

Third: After an employee has recovered from a heart attack, it is a basic responsibility of the
company medical programs to match the man to the job. This means that there must be a medical
evaluation of the job itself, as well as an evaluation of the employee's physical capabilities.

Our own experience shows that the employee who has received proper medical treatment for his
cardiovascular problems, who is placed in a job with requirements not inconsistent with his regi­
nary's improved performance of his duty.

The family history (Figure) disclosed that the father of

Case 1 (84454) —This child, a boy, was brought up on a formula of soy, peanu t oil, and cod liver oil.
He developed rhinitis and asthma, and had a history of recurrent attacks of pneumonia. At the age of 18 months, he had
had three more attacks of otitis media, each responding to

The report of a case of chronic bronchitis due to cow's milk

John W. Gerrard, DM

The child with recurrent rhinitis and bronchitis pre­
sents a common and sometimes perplexing problem. This

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O ne of the common problems facing both pedis­
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who seems to have one cold after another, each cold following by an attack of bronchitis or bron­
cho-pneumonia, often necessitating admission to hospital.1 The fundamental cause of the child's re­
peated respiratory tract infections frequently re­
 mains obscure, for though conditions such as cystic fibrosis of the pancreas and agammaglobulinemia may be suspected, there are no confirmatory tests. Some children with these symptoms grow this disorder, while asthma may develop in others.2 We have recently encountered four chil­
dren whose predisposition to recurrent respiratory tract infections was relieved by the simple expe­
cience of excluding cow's milk and dairy products from their diets; each child had one parent with

The child with recurrent rhinitis and bronchitis presents a common and sometimes perplexing problem. This disorder was seen in four children. Each child had one parent who was similarly affected. Four of the 11 siblings also had this syndrome. The four children together with their affected parents and siblings were all relieved of their symptoms when cow's milk and its products were eliminated from their diets.

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Familial Recurrent Rhinitis and Bronchitis Due to Cow's Milk

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tricians and family physicians is the child
who seems to have one cold after another, each cold following by an attack of bronchitis or bron­
cho-pneumonia, often necessitating admission to hospital.1 The fundamental cause of the child's re­
peated respiratory tract infections frequently re­
 remains obscure, for though conditions such as cystic fibrosis of the pancreas and agammaglobulinemia may be suspected, there are no confirmatory tests. Some children with these symptoms grow this disorder, while asthma may develop in others.2 We have recently encountered four chil­

The child with recurrent rhinitis and bronchitis presents a common and sometimes perplexing problem. This disorder was seen in four children. Each child had one parent who was similarly affected. Four of the 11 siblings also had this syndrome. The four children together with their affected parents and siblings were all relieved of their symptoms when cow's milk and its products were eliminated from their diets.