Special Communication

The Coronary Drug Project

Findings Leading to Discontinuation of the 2.5-mg/day Estrogen Group

The Coronary Drug Project Research Group

As noted in two previous reports from the Coronary Drug Project,[1,2] physicians face a difficult dilemma concerning pharmacologic therapy of hyperlipidemia-hyperlipoproteinemia in an attempt to prevent first or recurrent episodes of clinical coronary heart disease. It is known that susceptibility to premature coronary heart disease is directly related to serum levels of cholesterol, and of low-density and very-low-density lipoproteins. It is also known that elevated serum levels of lipids-lipoproteins frequently can be influenced over long periods of time by available drugs. However, answers to key questions about these pharmaceutical agents are lacking. Do they prevent coronary heart disease and prolong life? Are they reasonably safe in long-term usage?

The Coronary Drug Project—a nationwide collaborative study sponsored by the National Heart and Lung Institute—is the most extensive effort ever undertaken to answer these questions with regard to men who have already experienced one or more episodes of myocardial infarction.[1-5]

The present report deals with recent findings of the Coronary Drug Project that strongly indicate lack of therapeutic efficacy of the 2.5-mg/day mixed conjugated-equine-estrogen regimen, and that also suggest possible adverse effects. These results have led to discontinuation of this drug regimen in the project.

Methods

The background, design, and organization of the project were described in detail in earlier reports.[1-5] Its primary objective has been to test the efficacy and safety of several lipid-lipoprotein influencing drugs in the long-term therapy of coronary heart disease in men aged 30 to 64 years, with proven previous myocardial infarction. For this purpose, 8,341 patients were recruited by the 53 project clinical centers and were randomly assigned to six groups: conjugated estrogens, 2.5 mg/day (ESG1); conjugated estrogens, 5.0 mg/day (ESG2); clofibrate, 1.8 gm/day; dextrothyroxine sodium (Choloxin), 6.0 mg/day; niacin, 3.0 gm/day; and a lactose placebo. The numbers of men allocated to these treatment groups were 1,101, 1,119, 1,103, 1,110, 1,119, and 2,789, respectively. (As previously reported, the 5.0-mg/day estrogen regimen was discontinued in 1970 chiefly because of an excess number of nonfatal cardiovascular events in this group compared to placebo, and the dextrothyroxine group was discontinued late in 1971 because of an excess number of deaths compared with the placebo group, particularly among those of higher risk at base line.[1,2]

The first man was randomly allocated to treatment in March 1966 and the last of the 8,341 men in October 1969. The mean date for randomization was June 1, 1968. The data reviewed in this report are as of Feb 1, 1973, and represent a mean length of time of almost five years (56 months) since randomization. Seventy-six percent of patients have been in the study for at least four years and 33% for at least five years.

Patients randomized in this study were men aged 30 through 64 years, with documented evidence of one or more myocardial infarctions, categorized as class I or II of the functional classification of the New York Heart Association,[6] and free from a specified list of diseases and conditions. All patients were confirmed to be both at least three months beyond their most recent myocardial infarction and free of evidence of recent worsening of their coronary disease or of other major illnesses. They were also classified as to risk. Risk 1 included men with a single myocardial infarction, free of defined serious complications during the acute episode. Risk 2 included men with two or more myocardial infarctions and those with a single myocardial infarction who, during the acute episode, did have one or more defined complications (eg, pericarditis, congestive failure, shock, arrhythmia, or extension of infarction).

A separate random allocation schedule was utilized by the Coordinating Center for each of the two risk groups within each participating clinic. Each schedule was designed to assure both approximately equal numbers of patients in the five drug groups and approximately five patients in the placebo group for every two patients in any of the other groups.

The study is double-blind in the sense that neither the patient nor the clinic staff is informed of the patient's drug allocation, except as may be required in a verified medical emergency. Initial prescription of assigned medication was three capsules per day, supplying one third of ultimate full dosage, with an increase at monthly intervals to six and then to the full dosage of nine capsules per day, unless the managing physician altered the regimen for specified reasons.

Each patient is to be observed for

For a complete list of the key bodies of the Coronary Drug Project and senior staff members see p 657.

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Table 1.—Nonfatal Events and Deaths by Cause

Event	ESG1 No. of Men	ESG1 No. With Events	ESG1 %	Placebo No. of Men	Placebo No. With Events	Placebo %	Z Value	RBO, .25	RBO, min
Death									
All causes	1,101	219	19.9	2,789	525	18.8	0.76	5.82	1.00
All cardiovascular*	1,101	190	17.3	2,789	481	17.2	0.01	7.61	1.00
All noncardiovascular	1,101	23	2.1	2,789	35	1.1	1.93	0.83	0.83
Cause unknown	1,101	6	0.5	2,789	9	0.3	1.01	1.09	1.00
All coronary heart disease	1,101	162	14.7	2,789	410	14.7	0.01	6.29	1.00
All sudden cardiovascular	1,101	82	7.4	2,789	246	8.8	−1.39	1.77	0.91
All cancer	1,101	14	1.3	2,789	13	0.5	2.73	0.28	0.09
Lung cancer	1,101	6	0.5	2,789	4	0.1	2.23	0.72	0.38
Definite nonfatal myocardial infarction	1,059	121	11.4	2,693	306	11.4	0.05	2.46	0.92
Myocardial infarction incidence (definite nonfatal myocardial infarction or coronary death)	1,101	256	23.3	2,789	652	23.4	−0.08	4.86	1.00
Definite fatal or nonfatal pulmonary embolism	1,101	17	1.5	2,789	22	0.8	2.13	0.43	0.32
Definite or suspected fatal or nonfatal pulmonary embolism or thrombophlebitis	1,101	52	4.7	2,789	82	2.9	2.75	0.19	0.17

*Excludes sudden deaths attributed to noncardiovascular causes.

Table 2.—Percentage of All Deaths, by Cause

Cause of Death	ESG1 No. of Deaths	ESG1 %	Placebo No. of Deaths	Placebo %
All causes	219	100.0	525	100.0
Total Cardiovascular	190	86.8	481	91.6
Coronary	162	74.0	410	78.1
Cerebrovascular	4	1.8	11	2.1
Pulmonary embolism	2	0.9	6	1.1
Congestive heart failure	10	4.6	17	3.2
Other cardiovascular	12	5.5	37	7.0
Noncardiovascular	23	10.5	35	6.7
Cancer	14	6.4	13	2.5
Noncancer	9	4.1	22	4.2
Cause unknown	6	2.7	9	1.7
Sudden (cardiovascular only)	82	37.4	246	47.4

Table 3.—Cancer Deaths by Anatomical Site

Site	ESG1 (1,101 Men) No. of Deaths	ESG1 (1,101 Men) %	Placebo (2,789 Men) No. of Deaths	Placebo (2,789 Men) %	Z Value
All sites	14	1.27	13	0.47	2.73
Lung	6	0.54	4	0.14	2.23
Brain	1		0		
Stomach	2		0		
Liver, gallbladder	1		2		
Pancreas	2		1		
Kidney	0	8 0.73	1	9 0.32	1.72
Prostate gland	1		1		
Blood, lymph	0		2		
Primary site unknown	1		2		

Table 4.—Cancer Mortality by Cigarette Smoking Status at Entry

Smoking Status	ESG1 No. of Men	ESG1 No. of Deaths	ESG1 %	Placebo No. of Men	Placebo No. of Deaths	Placebo %	Z Value
All cancer deaths							
Nonsmoker	669	6	0.90	1,731	6	0.35	1.71
Smoker	432	8	1.85	1,058	7	0.66	2.09
Lung cancer deaths							
Nonsmoker	669	3	0.45	1,731	1	0.06	2.10
Smoker	432	3	0.69	1,058	3	0.28	1.14

a period of at least five years. He reports to the clinic every four months for a follow-up visit. A complete standardized examination, including a resting electrocardiogram, is made annually. Complaints and findings suggestive of illness or toxic reaction are thoroughly evaluated by the research clinic. In all circumstances, the Coronary Drug Project Protocol and Manual of Operations allow full leeway for optimal long-term medical care for patients with a history of myocardial infarction.

Data in a standard format are sent to the Coordinating Center and are continually monitored for "events," including death by cause, recurrent myocardial infarction, congestive heart failure, intermediate coronary episodes called acute coronary insufficiency, angina pectoris, electrocardiographic changes, stroke, venous thromboembolism, and hospitalization by cause. In addition, data are monitored for drug side-effects such as gynecomastia, breast tenderness, loss of libido, flushing, nausea, jaundice, insomnia, tremor, or deviations of serum enzyme levels from base line values.

One of the major challenges facing the Coronary Drug Project has been in the area of the techniques to be used for statistical evaluation of observed differences between an individual treatment group and the placebo group. The usual approach to tests of significance—eg, declaring a z value (difference between two proportions divided by the standard error of the difference) of 2 as significant with $P=.05$—has definite limitations in application to a study of this type. The difficulties in applying these tests stem from at least four specific design features of the project: its effort to evaluate five treatment groups simultaneously rather than merely one; the need to review end point data at frequent intervals throughout the study, to detect any beneficial or adverse therapeutic effects as soon as possible; the need to evaluate several fatal and nonfatal end points simultaneously; and the need to evaluate treatment differences within subgroups of patients. This multiplicity of statistical tests makes it certain that usual tests will too frequently result in statistical "significance" ($P=.05$ or less) when in fact no truly

significant difference from placebo exists. In an attempt to cope at least partially with this problem, two approaches for evaluation of statistical significance were developed by project statisticians. One is a modification of sequential statistical testing procedures, the other is a Bayesian approach yielding a numerical value designated RBO (relative betting odds).[1,2,7,8] Both methods are more stringent than usual significance tests in terms of differences between an experimental and a control group required to designate statistical "significance."

At a special combined meeting of the Data and Safety Monitoring Committee and the Steering Committee in early March 1973, extensive reviews were made of the latest available data relating to all end points under surveillance. These data, generated by the Coordinating Center in preparation for the regular semiannual meeting of the Data and Safety Monitoring Committee (scheduled for April 1973), were deemed of sufficient concern by the leadership of the study and the National Heart and Lung Institute to warrant the special meeting convened in early March.

As a result of this evaluation, the joint session of the Data and Safety Monitoring Committee and the Steering Committee unanimously recommended discontinuation of ESG1. This recommendation was promptly reviewed and ratified by the Policy Board, approved by the Technical Group, and implemented.

Results

Comparability at Entry of the ESG1 and Placebo Groups.—As previously reported,[3] detailed univariate and multivariate analyses revealed that the randomization procedure fulfilled its objective of yielding two groups comparable at entry. There is no evidence that any differences in morbidity and mortality rates developing in the years since onset of the study can be attributed to original differences in risk of the two groups.

Morbidity and Mortality.—MORTALITY FROM ALL CAUSES.—As of Feb 1, 1973, with an average length of patient follow-up of 56 months, the proportion of deaths from all causes in the ESG1 group was 19.9%; in the placebo group, it was 18.8% (Table 1).

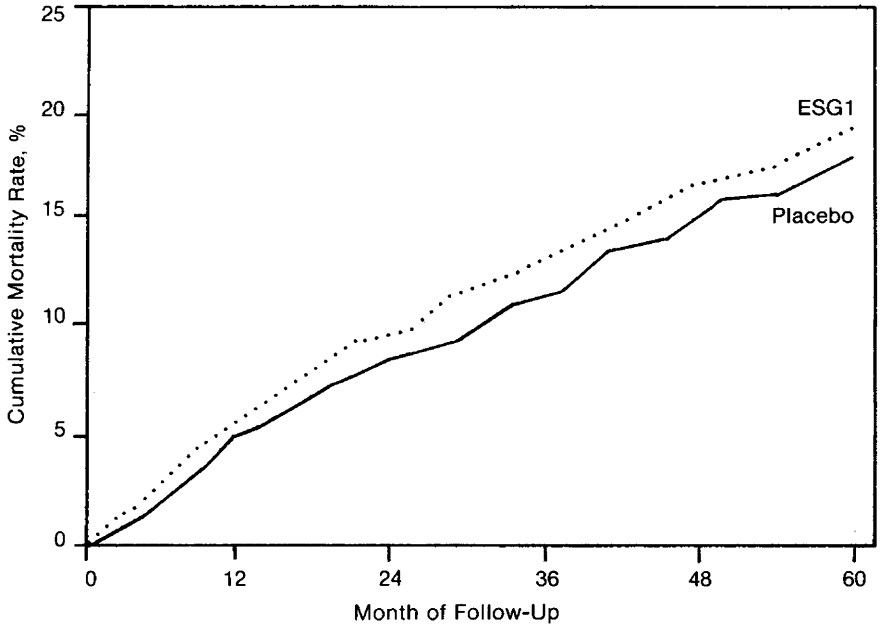


Fig 1.—Life-table cumulative rates for deaths from all causes for ESG1 and placebo groups.

This small difference in proportions—in the order of 5.8% (1.1/18.8)—does not approach statistical significance even by usual statistical tests ($z=0.76$).

Analysis by the life-table method revealed that the small absolute difference in favor of placebo emerged early in the study and persisted at a fairly constant level of about 1.0 percentage point after the second year of follow-up (Fig 1).

Analyses were also performed by two methods to assess the possibility still remaining of a statistically significant outcome for six-year mortality favoring ESG1 treatment at the planned termination of the regimens in October 1974. Both these methods indicated that a dramatic and unlikely change in the mortality pattern for ESG1 patients would be required.

Further, when the data were subclassified by age (<55 and ≥ 55) and risk (1 or 2, as earlier defined), actual ESG1 mortality experience is somewhat but not significantly worse than placebo experience for three of the four subgroups. For one subgroup (age ≥ 55, risk 2) ESG1 has a slightly but insignificantly better mortality experience than placebo.

These results constitute a strong case for concluding that ESG1 therapy is not effective with respect to the main project end point—total mortality.

CAUSE-SPECIFIC MORTALITY AND MORBIDITY.—As is evident from Table 1, mortality from all cardiovascular causes and from coronary heart disease was similar in the two groups. The proportion of sudden cardiovascular deaths (ie, cardiovascular deaths occurring within 60 minutes after the onset of symptoms) was slightly but not significantly ($z=1.39$) lower in the ESG1 group than in the placebo group, 7.4% and 8.8%, respectively. For definite nonfatal myocardial infarction and for myocardial infarction incidence (definite nonfatal myocardial infarction or coronary death), the proportions were nearly identical for the two groups.

Incidences of definite fatal or nonfatal pulmonary embolism, and of definite or suspected fatal or nonfatal pulmonary embolism or thrombophlebitis, were distinctly higher for the ESG1 group than for the placebo group (Table 1). However, the differences were not statistically significant by the RBO procedure.

Mortality from all cancers was higher for the ESG1 than the placebo group (1.3% and 0.5%, respectively), a difference that was statistically significant by classical methods ($z=2.73$, $P=.006$), but not by either the RBO or the sequential testing procedure (Table 1, Fig 2).

As is indicated from Table 2, for both the ESG1 and placebo groups the

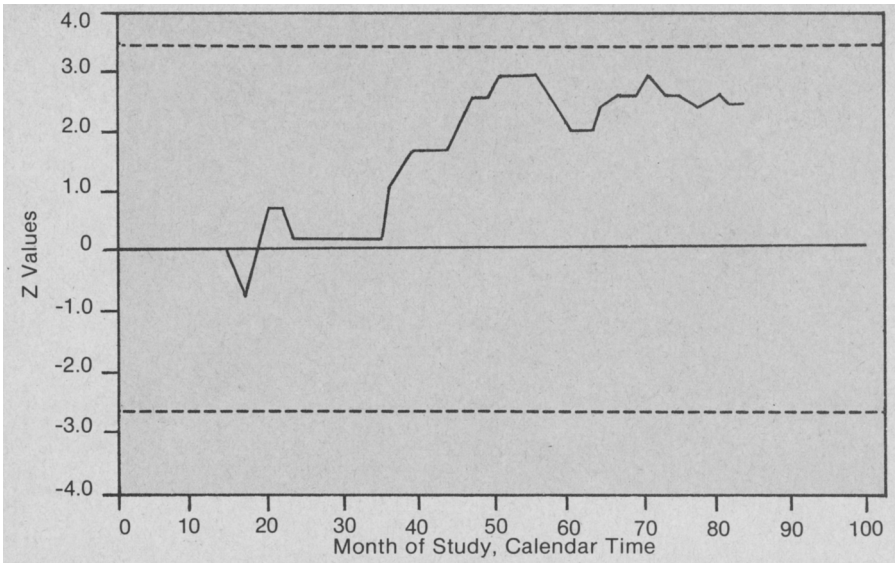
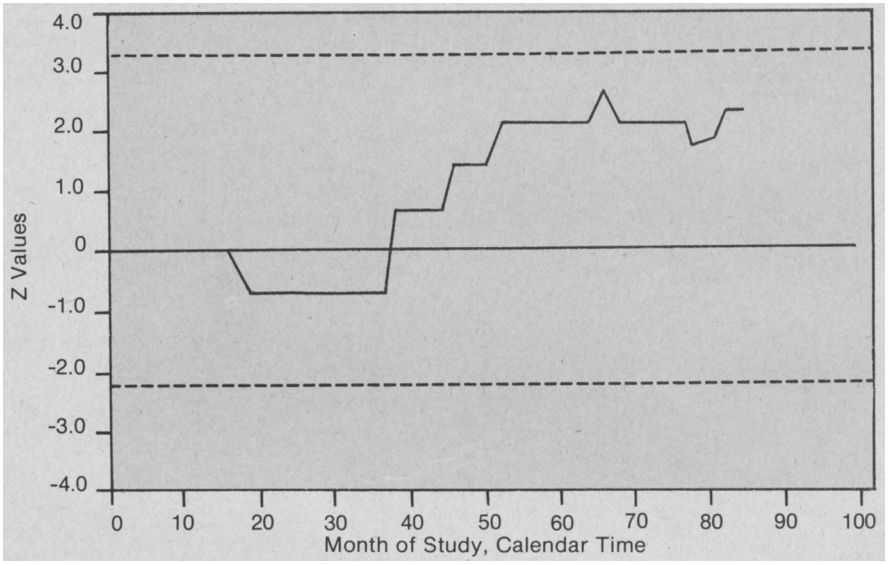


Fig 2.—Z values for observed ESG1-placebo differences in proportion of cancer deaths, and sequential boundaries (dotted lines) for the .05 level of significance.

Fig 3.—Z values for observed ESG1-placebo differences in proportion of deaths from lung cancer, and sequential boundaries (dotted lines) for the .05 level of significance.



great majority of deaths (86.8% and 91.6%, respectively) were attributed, as expected among men recovered from one or more myocardial infarctions, to cardiovascular causes; 74.0% and 78.1%, respectively, were coronary deaths; 37.4% and 47.4%, respectively, were sudden cardiovascular deaths. In contrast to these lower proportions of cardiovascular deaths in the ESG1 group, the proportion of all deaths attributed to cancer was higher for the ESG1 group than for the placebo group (6.4% and 2.5%, respectively). Data on malignant neoplasms not fatal to date will be reported subsequently.

DETAILED ANALYSIS OF CANCER MORTALITY.—Of the 14 cancer deaths among 1,101 men in the ESG1 group, six (42.9%) were described as malignancies of the lung; of the 13 cancer deaths among the 2,789 men in the placebo group, four (30.8%) were described as malignancies of the lung (Table 3). The mortality figures for lung cancer were 0.54% and 0.14% for the ESG1 and placebo groups, respectively, ie, a figure approximately four times as high for the former group. The difference in proportions has a z value of 2.23 with a P value of .026 by classical statistical test (Table 1). However, the two more rigorous methods for testing significance—ie, the sequential boundaries and the Bayesian procedures—indicate that the difference does not attain the .05 level of significance (Table 1, Fig 3).

No other apparent site of predilection for fatal neoplasm was observed (Table 3). No deaths from breast cancer were reported.

Data on all cancer and lung cancer mortality by cigarette smoking status at entry are presented in Table 4. Over the course of the study, smoking habits remained similar in the two groups; only a small percent of the men smoking cigarettes at entry quit thereafter. Higher proportions of cancer deaths were observed for the ESG1 group compared to the placebo group for both nonsmokers and smokers. Two of the comparisons—all cancers in smokers and lung cancer in nonsmokers—yielded P values at the .05 level by classical tests. Data on histologic type of lung cancer will be reported subsequently.

Side-Effects.—The ESG1 patients, despite the low dosage of mixed conjugated equine estrogens, frequently developed the usual side-effects of the hormone—eg, testicular atrophy, gynecomastia, vascular spiders, and loss of libido and potency. On the other hand, prostatic abnormalities were reported less frequently for the ESG1 group than for the placebo group. The feminizing side-effects of estrogen led to a higher rate of dropout and reduced adherence for the ESG1 group.

Biochemical and Hematologic Findings.—Several differences between the ESG1 and placebo groups were noted with respect to biochemical and hematologic findings—eg, lower levels of serum bilirubin, serum glutamic oxaloacetic transaminase, alkaline phosphatase, uric acid, and hematocrit in ESG1 men. The mean cholesterol level of the ESG1 group was reduced slightly from base line levels; serum triglyceride content increased with ESG1 treatment.

Comment

With an average follow-up of 56 months in the Coronary Drug Project as of Feb 1, 1973, there is no evidence of therapeutic efficacy in regard to the key end point of total mortality for the group of men receiving ESG1.

Moreover, there are strong statistical indications that no such evidence can be forthcoming by the originally planned date of regimen termination in October 1974. At the same time, there are trends suggestive of deleterious effects, particularly in regard to two sets of cause-specific end points—incidence of pulmonary embolism and thrombophlebitis, and mortality from all cancers and lung cancer. While these trends are not statistically significant by the tests utilized in the project, it was deemed appropriate to discontinue this treatment regimen in the project—especially in view of lack of evidence of countervailing beneficial effect with this medication, the improbability of such a positive effect over the next years, the troublesome side-effects and associated poor adherence, and the determination of the project to minimize risk of deleterious effects in study patients.

The findings, with respect to possible increased risk of venous thromboembolic disease for the ESG1 group, are consistent with an earlier report of higher incidence of nonfatal pulmonary embolism and thrombophlebitis for the ESG2 group.[1] This latter regimen was discontinued after an average of 18 months of follow-up because of that complication, as well as a higher incidence of nonfatal myocardial infarction, without concomitant evidence of beneficial influence on mortality.[1] These findings on increased risk of venous thromboembolic disease in men receiving exogenous estrogens are also consistent with other reports of similar complications in men and women receiving this medication, eg, for treatment of prostatic carcinoma or for contraceptive purposes.[1,9,10]

The results suggestive of higher mortality rates from all cancers, and from lung cancer in the ESG1 group, require detailed further evaluation, since thus far only cancer mortality has been reported, without reference to nonfatal cancer, date of diagnosis of the cancer, circumstances surrounding the diagnosis, or histopathologic type. Further information is being collected from the clinics and detailed analyses are being carried out on cases of nonfatal and fatal neoplastic disease, and the specific histopathologic findings, in both ESG1 and ESG2 patients, as well as placebo patients. The results of these more detailed investigations will be reported at an early date. All three of these groups (ESG1, ESG2, and placebo) will be kept under long-term surveillance to collect further data on malignant disease.

Summary

The Coronary Drug Project is a national collaborative study to evaluate long-term effects of several drug regimens influencing lipid metabolism, compared with placebo, in men originally aged 30 to 64 years who had recovered from one or more episodes of myocardial infarction.[3] From 1966 to 1969, the 53 clinical centers recruited 8,341 patients who were randomly assigned to the project's six groups.

As previously reported, two of the study regimens—5.0 mg/day of estrogen (ESG2) and 6.0 mg/day of dextrothyroxine (DT4)—were discontinued in 1970 and 1971, respectively, because of trends indicative of adverse effects.[1,2]

As of Feb 1, 1973, with an average follow-up of 56 months, data on the 2.5-mg/day estrogen group (ESG1) indicated no evidence of an overall positive therapeutic effect in terms of the project's primary end point, mortality from all causes. Rather there was a small, statistically insignificant excess of total mortality in the ESG1 group compared to the placebo group (19.9% vs 18.8). Statistical analyses demonstrate that emergence of a mortality trend indicative of therapeutic efficacy for the ESG1 group is highly improbable. Furthermore, based on small numbers of cases in both the ESG1 and placebo groups, there are suggestions of adverse trends with this estrogen regimen, in the form of excess incidence of venous thromboembolism (including pulmonary embolism) and excess mortality from all cancers and particularly from lung cancers. A high incidence of troublesome side-effects has also been recorded in the ESG1 group, with associated poor adherence.

Based on these findings, the Coronary Drug Project has discontinued the ESG1 regimen and removed all patients from this medication. This decision is in conformity with the determination and concern of the Coronary Drug Project research group to minimize possibilities of subjecting study patients to potential harm.

All patients who had received estrogens in the program—both those on the discontinued ESG1 and ESG2 regimens—are being followed up long-term and compared with the placebo group to assess possible residual unfavorable effects. Further detailed findings for these groups will be reported, particularly with regard to nonfatal and fatal malignant neoplasms and their histopathologic types.

All data from the study for the two remaining active treatment groups—clofibrate (1.8 gm/day) and niacin (3.0 gm/day)—are continuing to be reviewed comprehensively at regular intervals for possible adverse trends as well as beneficial effects.

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JAMA
75 YEARS AGO

Nov 5, 1898

Why Should We Estimate for Urea

We have been taught that the excretion of uric acid to urea stands in the relation of 1 to 33. HAIG states: "My researches have extended over a large part of the last twelve years, but taking only the figures of the longer periods of my estimation of my own excretion, we get a total of 2351 days, in which 28,447 gr. of uric acid, 805,432 gr. of urea and 127,725 of acid (reckoned as oxalic acid) were excreted, giving a relation of uric acid to urea of about 1 to 28, and a relation of acid to urea of 1 to 6.3."

If we desire to estimate the amount of uric acid in a given sample of urine, and turn to the process first devised by HOPKINS, we might be astounded at the lengthened process necessary to obtain the amount of such a common ingredient as uric acid. Indeed, the quantitative estimation is hardly ever resorted to at the present day, on account of its tediousness and certain errors which might ensue from the expertness required in making the estimation. The simple quantitative method of precipitating the uric acid by acidulating the urine with hydrochloric acid and collecting on an equipoised filter is also open to serious and fallacious results. Therefore, it saves time and trouble to say that the daily excretion of uric acid to urea stands in the relation of 1 to 33 and, after estimating the amount of urea, it is an easy matter to compute the amount of uric acid excreted daily in a given quantity of urine.

The specific gravity method is also simple in estimating the amount of urea. For instance, a method is given which states that: "A given specimen of urine, neither albuminous nor saccharin, containing a normal proportion of chlorids, and having a specific gravity of 1020–4 is a quantity of 1500 c.c. (50 oz.) in twenty-four hours, may be taken as a standard normal specimen containing 2 to 2.5 per cent. of urea. These conditions being observed, a higher specific gravity would indicate an increased proportion, and a lower a diminished proportion. Under these circumstances, a specific gravity of 1014 indicates about 1 per cent. of urea and of 1028 to 1030 about 3 per cent." Here again there is room for unbounded fallacy.

But what of the more accurate methods for the estimation of urea, as now taught by the foremost medical colleges? DAVY'S method, which depends upon the decomposition of urea by means of sodium hypochlorite, has certain objections, because it is stated that NaClO in the presence of caustic alkalies causes the evolution of only one-half of the nitrogen of urea, the remainder being retained as a cyanate. With the KJELDAHL method the writer has had no experience. The method, however, which seems to be the favorite is that known as the "hypobromite," and depends upon the decomposition of the urea in the urine by means of sodium hypobromite (NaBrO), with the production of sodium bromid (NaBr), water, carbon dioxid (CO_2) and the evolution of nitrogen. After correcting for temperature and barometric pressure, the nitrogen in the hypobromite method can probably be most accurately estimated. Suppose that we have before us a given specimen of urine and we desire to find the amount of urea by the hypobromite method and, after completing the examination in detail, we find the amount of urea present in this given specimen. It is true, we have at last obtained the correct data in regard to the amount of urea in the urine, but it is also true that we have not determined the amount of metabolic activity nor the amount of animal food eaten the day before by the patient, and upon these factors depends the average normal amount of urea in the urine. Therefore it is hard to devise a *standard* normal amount of urea, because it varies with katabolism and with the amount of animal food giving a great amount of urea, and vice versa. . . .

Since the normal amount of urea in the urine depends upon katabolic activity and upon the amount of nitrogenous food ingested, and since this normal amount is so variable, we may well ask of what real benefit is the estimation of urea in the urine?