NORMAL PLASMA CHOLESTEROL IN A MAN WHO EATS 25 EGGS A DAY

To the Editor: Dr. Kern's report (March 28 issue)* of an elderly man with normal cholesterol levels who eats more than two dozen eggs a day is interesting, especially to those of us with an interest in cholesterol metabolism. I do, however, note that the patient was described as having an extremely poor memory and had been given a diagnosis of Alzheimer's disease and intermittent depression. The patient was then said to have given written informed consent for the study. Although the nature of the study was apparently extremely benign, I would question the capacity of persons with Alzheimer's disease and extreme memory deficits to give informed consent.

DAVID SCOTT, M.D.
Minneapolis, MN 55416 Park Nicollet Medical Center

*Kern F Jr. Normal plasma cholesterol in an 88-year-old man who eats 25 eggs a day: mechanisms of adaptation. N Engl J Med 1991; 324:896-9.

To the Editor: Kern's report of the 88-year-old man whose daily diet included 25 eggs suggests that this diet antedated the study by 15 years, but Kern fails to describe any other components. Intake is presumed to be isocaloric, since no weight changes were noted. On the basis of this assumption, the metabolic needs of a 6-ft 1-in., 185-lb man range from 2080 to 2351 calories per day. Twenty-five eggs provide 1875 calories, or 80 to 90 percent of his energy requirement. How the remaining 200 to 500 calories ingested per day managed to prevent major nutritional deficiencies in this man is curious.

A computer analysis compared the nutritional content of the eggs with nutritional needs* and identified inadequacies in the levels of carbohydrates (5 percent of total calories), niacin (6 percent of the recommended daily allowance [RDA]), copper (7 percent of the RDA), ascorbic acid (0 percent of the RDA), and fiber (0 percent of the RDA) provided. The diet provided megadoses of some nutrients, including selenium (443 percent of the RDA).

How this man managed to escape any nutritional consequences of his limited diet can be ascertained only by learning details of the rest of his daily intake, since man does not live by egg alone.

MIRIAM ERICK, R.D.
Boston, MA 02115 Brigham and Women's Hospital

*The food processor II: nutrition & diet analysis system version 3.0. Salem, Oreg.: ESHA Research, 1990.

To the Editor: The paper by Kern has received considerable publicity, with news reports suggesting that the study shows that cholesterol is unimportant, without discriminating between cholesterol in the diet and that in the blood. Dietary cholesterol has an important effect on the cholesterol level in the blood of chickens and rabbits, but many controlled experiments have shown that dietary cholesterol has a limited effect in humans. Adding cholesterol to a cholesterol-free diet raises the blood level in humans, but when added to an unrestricted diet it has a minimal effect. Publicizing the story of a man who ate 25 eggs a day will ultimately confuse the public and instill skepticism about nutritional teaching, an area in which emphasis on the fatty acids in the diet is needed.

ANCEL KEYS, PH.D.
Minneapolis, MN 55455 University of Minnesota

The above letters were referred to Dr. Kern, who offers the following reply:

To the Editor: I share Dr. Scott's concern about the importance of informed consent in clinical investigation. Despite the truly benign nature of our studies, as noted by Dr. Scott, my colleagues and I did make repeated efforts to reinforce the signed consent by telling the patient that we were interested in examining his cholesterol metabolism in order to help us understand his good health in the presence of his unusual dietary habit. Because of his poor memory, we explained this to him every time we drew blood. Although memory loss was the only apparent clinical feature of his Alzheimer's disease, I cannot be certain about the depth of his understanding. He had no living relative to assume responsibility for him.

Ms. Erick's point about the nutritional inadequacy of an egg diet is valid. The patient's dietary history, confirmed by personnel at the retirement community, revealed that his diet was general, consisting of fruits, vegetables, cereals, and meats, but the quantity of these other foods obviously was quite limited. Because of this, his physician had been treating him with vitamin supplements for many years, which may well explain the absence of nutritional deficiency.

Dr. Keys notes the often inaccurate publicity concerning the importance of dietary cholesterol. This is regretable, but we did everything we possibly could to avoid incorrect interpretation of this study. The major purpose of the study was to identify the physiologic and biochemical processes involved in the patient's responses to a huge amount of cholesterol in his diet.

FRED KERN, JR., M.D.
Denver, CO 80262 University of Colorado School of Medicine

CARDIAC ARRHYTHMIA SUPPRESSION TRIAL

To the Editor: The investigators of the Cardiac Arrhythmia Suppression Trial (CAST) (March 21 issue)[1] found an excess of deaths due to arrhythmia and deaths due to shock after acute myocardial infarction in patients treated with encainide or flecainide. They concluded that the mechanisms underlying the excess mortality were unknown. However, clinical pharmacologic calculations may help to explain the results.

Encainide and flecainide are partly eliminated by the cytochrome P-450 system in the liver. They are poorly metabolized by approximately 7 percent of the U.S. population ("poor metabolizers"),[2] causing the drugs to be eliminated more slowly by other mechanisms. In poor metabolizers, encainide has bioavailability of 83 percent, a half-life of 11.3 hours, and a volume of distribution of 175 liters (body weight, 70 kg).[2] If they received the minimal dose used in the CAST study (35 mg three times daily), the theoretical maximal amount in the body at steady state would be 74.9 mg, corresponding to a maximal concentration of 428 ng per milliliter, an average concentration of 338 ng per milliliter, and a minimal concentration of 262 ng per milliliter.[3] The effective antiarrhythmic concentration is 220 ng per milliliter.[2] Similar calculations for flecainide also show that poor metabolizers are intoxicated even by the low dose. Several drugs are known to interact with encainide and flecainide during metabolism. For example, cimetidine may cause an "extensive metabolizer" to become a poor metabolizer. Arrhythmogenicity depends on the concentration of the antiarrhythmic drug.[4,5]

How did the CAST project guard against the risk of intoxication in about 7 percent of the 755 patients treated with encainide and flecainide (i.e., about 50 patients)? How many patients received drugs known to reduce the hepatic elimination of encainide or flecainide? Was therapeutic drug monitoring used? Supposing that many of the 50 poor metabolizers died of arrhythmia due to intoxication, it would be difficult for the study to show a beneficial effect of encainide and flecainide, since only 16 patients in the placebo group died of arrhythmia.

In extensive metabolizers, flecainide has bioavailability of 70 percent, a half-life of 11.0 hours, and a volume of distribution of 343 liters (body weight, 70 kg).[2] If they received the maximal dose used in the CAST study, the theoretical maximal amount in the body at steady state would be 198 mg, corresponding to a maximal concentration of 577 ng per milliliter, an average concentration of 405 ng per milliliter, and a minimal concentration of 271 ng per milliliter.[3] The therapeutic range is 400 to 800 ng per milliliter. If the dose is immediately absorbed and distributed, the plasma concentration would remain in the therapeutic range for only 5 hours and 49 minutes. Thus, the maximal dose seems to be insufficient during about half the day. The levels in the patients receiving the low dose would not even reach the therapeutic range, since the maximal theoretical concentration at steady state is 385 ng per milliliter. We are aware that each patient had a reduction in the initial arrhythmia of at least 80 percent, but would like to know why the dose schedules were so cautiously planned that the levels in the majority of patients probably did not reach the therapeutic range.