represent a large population who may be at very high risk for cardiovacular disease. Perhaps increasing the activity of the disabled makes more public health sense than trying to turn sedentary workers into Sebastian Coes.

Supported by grant from Alcoholic Beverage Medicine Research Foundation.

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HYPER-RESPONSE TO DIETARY CHOLESTEROL IN MAN

SIR,—In animals the response of serum cholesterol to dietary cholesterol is genetically determined,[1] and non-responders, with only small changes in serum cholesterol after dietary cholesterol, and hyper-responders have been defined. In man response to cholesterol in the diet is very varied[2] but since dietary challenge is usually done only once the reproducibility of the response is not known and the existence of human hyper-responders remains uncertain. Hyper-response to dietary cholesterol in man would be important because genetic disorders, such as familial hypercholesterolaemia and combined hyperlipidaemia, account for only a small percentage of the hypercholesterolaemia found in affluent populations.

We reinvestigated 17 men and 17 women (aged 23–78) who habitually consumed at least one egg a day and had participated in a trial in 1976.[3] Blood sampling and serum cholesterol analysis were standardised.[4] Serum cholesterol was measured twice on the egg-rich diet and again after 3 weeks during which the subjects ate no eggs or egg-containing products. Daily cholesterol intake on the two diets averaged 840 mg and 303 mg in 1976 and 811 mg and 245 mg in 1982. Mean serum cholesterol values fell by 0·16±0·42 mmol/l in 1976 (range −1·27 to +0·51) and by 0·31±0·35 mmol/l in 1982 (range −0·94 to +0·48). Individual responses in 1976 and 1982 were correlated ($r=0·32$, $p<0·05$), suggesting that part of the serum cholesterol response to dietary cholesterol is indeed individually determined.

This finding was confirmed in further studies. In the first experiment, ninety-four healthy men and women aged 18–72 consumed 10 mg cholesterol per MJ (on average 110 mg/day) for 14 days and 55 mg/MJ (610 mg/day) for another 14 days; blood was sampled twice on each diet. Almost all food was supplied by us and intakes were rigidly controlled.[5] Cholesterol (egg yolk) was the only dietary variable. The increased intake caused an increment in serum cholesterol concentrations of 0·50±0·39 mmol/l (mean ±SD), with individual responses ranging from −0·62 to +1·63 mmol/l.

Fifteen non-responders and seventeen hyper-responders, with increases of −0·01±0·21 and 0·96±0·27 mmol/l, respectively, were selected, and participated in the second trial 4 weeks later and the third trial 6 months later. The second experiment had the same design as the first. In the third experiment the subjects received 15 mg/MJ of cholesterol for 4 weeks and then 85 mg/MJ for another 4 weeks; blood was sampled six times on each diet. The serum cholesterol increased in the second trial by 0·06±0·35 mmol/l in the non-responders and 0·28±0·38 mmol/l in the hyper-responders; in the third trial these values were 0·47±0·26 and 0·82±0·35 mmol/l, respectively. The increases were almost entirely in the low-density lipoproteins. Again the response in each volunteer was only partly reproducible from one study to another, but the hyper-responders consistently showed a higher serum cholesterol response in the second and third trial than did the selected non-responders ($p<0·05$ and $p<0·005$, respectively).

CHANGES IN CHOLESTEROL LEVELS AFTER DAILY CONSUMPTION OF SIX EGG YOLKS

	% change* in volunteer					
—	A	B	C	D	E	F
1981						
Initial	+2	0	+4	+11	+6	−3
Final	+5	−3	+17	+17	+27	+5
1982						
Initial	−2	+1	+4	+13	−3	−1
Final	+16	+12	+26	+25	+4	+3

*% change from baseline serum cholesterol (mean of days −1 and 0) on days 1 and 2 (initial) and days 9 and 10 (final) of egg yolk added diet.

Since dietary measures would probably be effective only in hyper-responders, identification of such individuals would be desirable. To see if an egg-tolerance test could be used for this purpose six healthy volunteers age 27–43 years abstained from cholesterol-rich products for 10 days. For the next 10 days they were given six egg yolks per day (1500 mg cholesterol/day) besides their usual diet. The study was repeated a year later. Although the "final" (days 9 and 10) serum cholesterol was associated with the "initial" (days 1 and 2) value ($r=0·68$) suggesting that 2 days of excessive egg yolk consumption might help to identify hyper-responders, three volunteers (A, B, and E) showed responses from one year to another so different that a single 10-day experiment would give a misleading impression of sensitivity to dietary cholesterol (see table). Thus, although hyper-responders and non-responders to dietary cholesterol do exist in man, large intra-individual fluctuations in serum cholesterol[6] make it difficult to establish a person's true response.

Supported by the Netherlands Heart Foundation, grant 31.013 and an established investigatorship to M.B.K.

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HAEMORRHAGIC CYSTITIS AFTER LOW-DOSE CYCLOSPHOSPHAMIDE

SIR,—Haemorrhagic cystitis is a familiar complication of large doses of intravenous cyclosphosphamide. Hydration, with or without catheterisation and diuretic drugs, prevents it. Cystitis after low doses, although reported many years ago,[1,2] is not well-recognised, despite its disabling and sometimes fatal consequences. This prompts us to report our experience of four cases, including one reported in 1963.[2]

Case 1.—A man aged 34 with Hodgkin's disease, stage IVb, received oral cyclophosphamide 200 mg daily for 40 days (total dose 8 g), with no adverse effects. 1 week after the drug was stopped gross haematuria developed with pain, frequency, and sterile urine cultures. Intravenous urography demonstrated a small spastic bladder. With symptomatic treatment the pain and haematuria subsided after a month.

Case 2.—A man aged 23 with Hodgkin's disease, stage IVb, received intravenous cyclophosphamide 200 mg daily for 14 days

1. Clarkson TB, McMahan MR. Individual differences in the response of serum cholesterol to change in diet. In: Lauer R, Shekelle RB, eds. Childhood prevention of atherosclerosis and hypertension. New York: Raven Press, 1980: 127–35.
2 Connor WE, Connor SL. The key role of nutritional factors in the prevention of coronary heart disease. *Prev Med* 1972; **1:** 49–83
3 Bronsgeest-Schoute DC, Hermus RJJ, Dallinga-Thie GM, Hautvast JGAJ. Dependence of the effects of dietary cholesterol and experimental conditions on serum lipids in man III. The effect on serum cholesterol of removal of eggs from the diet of free-living habitually egg-eating people. *Am J Clin Nutr* 1979; **32:** 2193–97.
4 Katan MB, Van der Haar F, Kromhout D, Schouten FJM. Standardization of serum cholesterol assays by use of serum calibrators and direct addition of Liebermann-Burchard reagent. *Clin Chem* 1982; **28:** 683–86.
5 Van Raaij JMA, Katan MB, West CE, Hautvast JGAJ. Influence of diets containing casein, soy isolate, and soy concentrate on serum cholesterol and lipoproteins in middle-aged volunteers. *Am J Clin Nutr* 1982; **35:** 925–34.
6. Keys A Blood lipids in man: a brief review. *J Am Diet Ass* 1967; **51:** 508–16.
1. George P. Haemorrhagic cystitis and cyclophosphamide. *Lancet* 1963; ii: 942.
2 Spiers ASD Haemorrhagic cystitis and cyclophosphamide *Lancet* 1963; ii 1282–83.