DIET AND ATHEROSCLEROSIS

SIR,—The leading article (Nov. 1, p. 939) in which you discussed our trial of a diet high in unsaturated fat[1] made it clear that our report had not dealt adequately with at least one critical question. Specifically, your article suggested that the low incidence of atherosclerotic events in participants on the experimental diet might have been due to the chance inclusion of a smaller number of heavy cigarette smokers in that group than in the control group. In order to satisfy ourselves and others on this point, we have undertaken further analysis of our results in relation to smoking habits. The results of this analysis, reported below, provide convincing evidence that differences in smoking habits could not have accounted for the favourable experience of subjects on the experimental diet.

We have examined the question by stratifying the subjects on the basis of cigarette-smoking habits as reported at the time of entry into the trial. The outcome experience of the control and experimental groups was then compared within each stratum. Incidence of the primary end-point (ischæmic heart-disease manifested by sudden death or by definite myocardial infarction) was expressed in terms of subjects affected per 100 man-years. Incidence rates were also calculated for major end-points in combination.

1. Dayton, S., Pearce, M. L., Hashimoto, S., Dixon, W. J., Tomiyasu, U. American Heart Association Monograph no. 25. New York, 1969.

TABLE I—NUMBERS AND INCIDENCE-RATES OF MAJOR END-POINTS, STRATIFIED BY CIGARETTE-SMOKING HABITS AT ENTRY INTO THE TRIAL

Cigarette use at entry into study	Control group		Experimental group	
	No. of subjects	Incidence* per 100 man-years	No. of subjects	Incidence* per 100 man-years
Less than 10 cigarettes per day:				
No. of men in subgroup	166	..	164	..
S.D. or M.I.	25	2·45	21	2·02
S.D., M.I., or C.I.	32	3·13	25	2·40
Any " hard " end-point†	32	3·13	27	2·60
Fatal atherosclerotic events	20	1·95	18	1·73
10–20 cigarettes per day:				
No. of men in subgroup	129	..	173	..
S.D. or M.I.	22	2·56	20	1·76
S.D., M.I., or C.I.	30	3·49	21	1·85
Any " hard " end-point	34	3·95	25	2·20
Fatal atherosclerotic events	26	3·02	19	1·67
More than 20 cigarettes per day:				
No. of men in subgroup	70	..	45	..
S.D. or M.I.	13	2·86	5	1·70
S.D., M.I., or C.I.	17	3·73	6	2·04
Any " hard " end-point	20	4·39	6	2·04
Fatal atherosclerotic events	16	3·51	6	2·04
Not known:				
No. of men in subgroup	57	..	42	..
S.D. or M.I.	5	1·24	6	1·95
S.D., M.I., or C.I.	8	1·99	8	2·60
Any " hard " end-point	10	2·48	8	2·60
Fatal atherosclerotic events	8	1·99	5	1·62
All subjects:				
No. of men in group	422	..	424	..
S.D. or M.I.	65	2·37	52	1·87
S.D., M.I., or C.I.	87	3·18	60	2·16
Any " hard " end-point	96	3·51	66	2·38
Fatal atherosclerotic events	70	2·55	48	1·73

* A man with more than one event in the category cited was counted once only.

† Includes those events cited in the preceding footnote, plus the following: amputation of an extremity due to ischæmic gangrene, ruptured aneurysm, intestinal infarction.

S.D. = sudden death due to ischæmic heart-disease.

M.I. = definite myocardial infarction (overt or silent).

C.I. = definite cerebral infarction.

TABLE II—ESTIMATED " SMOKING-ADJUSTED " INCIDENCE OF MAJOR END-POINTS FOR TOTAL STUDY POPULATION

Clinical incident	Adjusted number of subjects affected		Adjusted incidence per 100 man-years	
	Control	*Exper.*	*Control*	*Exper.*
S.D. or M.I.	65·5	52·1	2·38	1·88
S.D., M.I., or C.I.	87·8	60·6	3·20	2·18
Any " hard " end-point	96·7	66·1	3·52	2·38
Fatal atherosclerotic events	70·9	48·3	2·58	1·74

As indicated in table I, at any of the three levels of cigarette consumption examined, the incidence of clinical events attributable to atherosclerosis was lower in experimental subjects than in individuals on the control diet. Thus when cigarette consumption is the same, the effect of the experimental diet persists.

Although table I makes it clear that there was a dietary effect, whatever the inequalities of the smoking distribution, it is also desirable to determine whether the surplus of heavy smokers in the control group accounted, *in part*, for the more favourable experience of the experimental group. Toward this end, we have developed estimates of "smoking-adjusted" incidence rates—that is, estimates of the outcome which would have resulted if the subjects of each smoking stratum had been allocated in equal numbers to the control and experimental groups. This was done by multiplying the number of subjects affected in a given cigarette-smoking stratum of the control group by $(E+C)/2C$, in which C = number of control subjects in the stratum and E = number of experimental subjects in the stratum; and by making a corresponding calculation for the experimental group. Resulting figures for all strata were totalled. Figures for total man-years at risk were similarly adjusted before calculating the adjusted incidence-rates. The objective of the calculation is to estimate the answer to this question: if a given stratum of a control group contains $1/2\,(C+E)$ subjects, whose mean experience is similar to that of the C subjects actually allocated to that subgroup; and if a corresponding experimental subgroup likewise contains $1/2\,(C+E)$ subjects, with mean experience comparable to that of the E subjects actually observed; and if this is true for all smoking strata, then what is the predicted outcome of such a trial? The resulting estimates, given in table II, are nearly identical to the figures actually observed (bottom of table I), the surplus of heavy smokers in the control group having been fully offset by an even larger surplus of moderate smokers (10–20 cigarettes per day) in the experimental group. We conclude, therefore, that the uneven distribution of cigarette-smoking habits had no net effect whatsoever on the outcome of the trial.

Returning to table I, the outcome in the control group reveals the well-known correlation between cigarette smoking and incidence of atherosclerotic complications. The smoking effect is not apparent, however, in the group on experimental diet; indeed, the experience of heavy-smoking experimental subjects was no worse than that of light-smoking and non-smoking subjects on either diet. Whether this is a true interaction between a dietary effect and smoking habits is difficult to judge with confidence on the basis of these observations. A true interaction of this nature, if confirmed by future work, would have important practical and theoretical implications. However, Leren's secondary-prevention trial[2] did not show evidence of interaction between the smoking effect and the diet effect. The reports of other dietary trials have not, to our knowledge, dealt with this question.

2. Leren, P. *Acta med. scand.* 1966, suppl. no. 466.

In referring to a "rebound" in serum-cholesterol level on resumption of normal diet by experimental subjects, your article conveys a disturbing misinterpretation of our observations. As indicated in fig. 20 of our report, we tested this question by selecting the 10 experimental subjects and the 11 control subjects who had had the best and most prolonged adherence. During the 8 months before termination of the experimental diet, these two subgroups had nearly identical mean serum-cholesterol concentrations. This must be attributed to chance, since the larger groups from which the sub-samples were drawn displayed lower mean levels among the experimental subjects than among the controls (see fig. 5 of our report). On resumption of the regular diet, the experimental subgroup displayed a prompt serum-cholesterol rise comparable in magnitude to the fall seen at the start of the study. Their levels were now higher than those of the control subgroup. This was surely not a "rebound" phenomenon, but rather an expression of the fact that *non*-dietary influences had set serum-cholesterol levels higher in these 10 experimental subjects than in the 11 men with whom they were compared.

Wadsworth Veterans Administration Hospital and U.C.L.A. School of Medicine, Los Angeles, California.

SEYMOUR DAYTON
MORTON LEE PEARCE.

POLYUNSATURATED FATTY ACIDS AND MYOCARDIAL INFARCTION

SIR,—Dr. Kingsbury and his colleagues (Dec. 20, p. 1325) make the following statement in their paper on polyunsaturated fatty acids and myocardial infarction: " Epstein also found no relationship between plasma-cholesterol or blood-sugar and new ischæmic events in patients with myocardial infarction over a similar three to four-year period ". I am afraid that this is a misquotation from the presentation to the Royal Society of Medicine.[1] Our data from the Tecumseh Community Health Study did not refer to such " new ischæmic events " but to new events among persons initially free of manifest disease. This, I hope, was quite apparent from the text. Moreover, it is incorrect to say that we did not find a relationship between plasma-cholesterol (or, rather, serum-cholesterol) and blood-sugar, as stated by Dr. Kingsbury and his associates. The actual findings, and some of their seeming inconsistencies, are carefully discussed in the original paper, and I do not want to impose on your space to recapitulate them. I will merely say that the numbers in the oldest and youngest age-groups amongst men were small, and so was the number of women who developed clinical events. Furthermore, the new clinical events identified in detail in my paper,[1] included angina pectoris and certain electrocardiographic ST-T wave changes which are less definite " endpoints " than heart attacks. Even so, coronary heart-disease and serum-cholesterol levels are, indeed, associated amongst men in the important 40–59 age-group. With regard to blood-sugar, the preliminary data in my paper to the effect that persons with high blood-sugar are preferentially prone to death has now been further substantiated.[2]

Surely, there is no reasonable doubt about the association between coronary heart-disease and serum-cholesterol.[3] Similarly, it seems to be more and more likely that hyperglycæmia is also a predisposing factor towards coronary disease.[4,5] It is only to be expected that there will be, from time to time, reports which are exceptions to the general rule that elevated cholesterol, or, for that matter, blood-pressure or glucose levels, predispose to ischæmic heart-disease. Acheson and Florey [6] have pointed out very well that a given predisposing factor is not necessarily operative in all ecological settings where multiple genetic and environmental influences interact. The urgent need is not so much to argue over these associations but to test, by means of preventive trials, whether they are causative.

To return to the paper by Dr. Kingsbury and his group, it is perhaps not surprising that they find no association between plasma-cholesterol and blood-sugar concentrations and the degree of arterial disease. After all, their subjects already had disease of such an advanced degree that they were patients attending the hospital with manifestations of peripheral atherosclerosis. Even though a biological factor may cause the gradual development of arterial disease, the extent of the disease in its late stages is not necessarily related to the level of this factor at this advanced stage. All this does not in the least detract from this and earlier work by Dr. Kingsbury on the possible importance of polyunsaturated fatty acids in the genesis of atherosclerosis.

School of Public Health, University of Michigan, Ann Arbor, Michigan 48104.

FREDERICK H. EPSTEIN.

1. Epstein, F. H. *Proc. R. Soc. Med.* 1967, **60**, 56.
2. Ostrander, L. D., Jr. Hyperglycemia and vascular disease in Tecumseh, Michigan. Proceedings of the First International Symposium on Early Diabetes, Marbella, Spain, Oct. 23–26, 1968. New York (in the press).
3. Epstein, F. H. *J. Am. med. Ass.* 1967, **201**, 795.
4. Epstein, F. H. *Circulation*, 1967, **36**, 609.
5. Epstein, F. H. *Minnesota Med.* 1969, **52**, 1271.

HEREDITARY HÆMORRHAGIC TELANGIECTASIA: AGGRAVATION BY ORAL CONTRACEPTIVES?

SIR,—We have seen three women with hereditary hæmorrhagic telangiectasia (H.H.T.) whose disease may have been aggravated by oral œstrogens.

A 46-year-old woman of Spanish descent, admitted for an unrelated cause, had had epistaxes since childhood, anæmia of undetermined cause since age 15, and facial telangiectasias and intermittent melæna since age 31. Her paternal grandfather had bled to death from a nosebleed; her father and two sons had typical cutaneous telangiectasias. $2^1/_2$ years ago she began oral contraceptives; six months later her facial lesions began enlarging, one becoming quite disfiguring; and one year ago epistaxes recommenced.

A review of hospital records of patients with H.H.T. revealed only one other who had been on oral contraceptives. This woman of 31 had telangiectasias of the skin and mucous membranes, and her mother had a history of epistaxes. The patient's epistaxes began 5 years ago, while she was taking ' Estinyl ' (ethinylœstradiol) for regulation of menstruation. They became worse during each of 3 pregnancies, and during the last, cautery was necessary 38 times. Despite a submucous resection, epistaxes continue to limit her activity.

Subsequently we saw a 42-year-old Mexican-American woman, whose mother and son had had troublesome epistaxes. She had been taking an oral contraceptive ' Ovo ' for 4 years. 2 years ago she noticed telangiectasias for the first time. Located on her finger tips and tongue, they have since grown larger, and frequently bleed on minor trauma. In the past year she has had occult gastrointestinal bleeding and anæmia.

The records of six other nearby hospitals (over 500,000 admissions) were searched for other instances of women with H.H.T. who were on oral contraceptives. None was found. Recently, however, one of us examined a Mexican-American woman with H.H.T. at Denver General Hospital before and repeatedly during the first 10 months of oral contraceptive therapy. Her lesions neither enlarged nor

6. Acheson, R. M., Florey, C. du V. *Lancet*, 1969, ii, 391.