Discussion

Sulphadimidine is a weak organic acid with a pK value of 7·34. The mechanisms which control its renal excretion are glomerular filtration (Weinstein 1965), proximal tubular secretion, tubular reabsorption (Weiner and Mudge 1964), and passive pH-dependent non-ionic back-diffusion (Milne 1967).

The present observations show that, within the range of glomerular filtration-rates of the subjects studied (2–134 ml. per minute), the renal clearance of sulphadimidine was independent of glomerular filtration-rate. In fact, the sulphadimidine clearance in the uræmic subjects was significantly higher than in the normal controls. This was due to a reduction of the serum-sulphadimidine levels in the uræmic subjects rather than an increase in the excretion-rate of the drug. Comty (1967) showed that total body-water is much increased in patients with end-stage kidney failure. The low serum-sulphadimidine levels in the uræmic subjects may in part have resulted from this since unbound sulphadimidine is distributed throughout the total body-water. Although the serum-sulphadimidine concentrations were reduced in the uræmic subjects, the excretion-rate of the drug did not differ significantly from that in the controls. The explanation for this surprising observation remains unknown. Possibly the tubular damage which existed in the uræmic subjects, as evidenced by the severe impairment of renal concentrating power, caused a reduction of tubular reabsorption of the drug. Whatever the explanation, the therapeutic implication of the present observations is evident—namely, that in patients with end-stage kidney failure sulphadimidine can be used for the treatment of urinary infections due to sensitive pathogens without fear of drug accumulation.

The present study also shows that in normal subjects the clearance of sulphadimidine is directly related to urinary pH. This finding accords with the observations of Dalgaard-Mikkelson and Poulsen (1956) on the clearance of sulphathiazole in pigs, and shows that pH-dependent non-ionic back-diffusion, as described by Milne et al. (1958), plays an important part in the renal handling of sulphadimidine in normal subjects.

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REFERENCES

Bratton, A. C., Marshall, E. K. (1939) *J. biol. Chem.* **128**, 537.
Brumfitt, W., Leigh, D. A., Percival, A., Williams, J. D. (1964) *Postgrad. med. J.* **40**, suppl. 1, p. 55.
Comty, C. M. (1967) *in* Proceedings of the European Dialysis and Transplant Association; vol. IV, p. 216. Amsterdam.
Dalgaard-Mikkelson, S., Poulsen, E. (1956) *Acta Pharmac. tox.* **12**, 233.
Garnett, E. S., Parsons, V., Veall, N. (1967) *Lancet*, i, 817.
Kunin, C. M. (1967) *Ann. intern. Med.* **67**, 151.
Milne, M. D. (1967) *in* Renal Disease (edited by D. A. K. Black); p. 546. Oxford.
— Scribner, B. H., Crawford, M. A. (1958) *Am. J. Med.* **24**, 709.
Weiner, I. M., Mudge, G. H. (1964) *ibid.* **36**, 743.
Weinstein, L. (1965) *in* The Pharmacological Basis of Therapeutics (edited by S. Goodman and A. Gilman); p. 1152. New York.

Preliminary Communications

CONTROLLED TRIAL OF A DIET HIGH IN UNSATURATED FAT FOR PREVENTION OF ATHEROSCLEROTIC COMPLICATIONS

Summary In a clinical trial of a diet low in saturated fat and cholesterol, and high in unsaturated fat of vegetable origin, carried out on 846 middle-aged and elderly men living in an institution, the subjects were allocated randomly to the experimental diet or to a control diet, and were followed double-blind. The combined incidence of myocardial infarction, sudden death, and cerebral infarction was significantly lower in the experimental group than in the control group. The incidence of fatal atherosclerotic events was also lower in the experimental group than in the control group, but total mortality-rates were similar for the two groups.

INTRODUCTION

IT has been known for some time that replacement of predominantly saturated fat in the diet by highly unsaturated fat such as that of vegetable oils can lower the serum-cholesterol concentration.[1 2] However, it has not been satisfactorily established that such diets modify the incidence of ischæmic heart-disease and other complications of atherosclerosis.

In 1959 we began a controlled institutional trial under double-blind conditions to test this question. The results are described herein.

MATERIAL AND METHODS

Male veterans, aged 54–88 years (mean 65·5 years), living in the domiciliary unit of the Los Angeles Veterans Administration Center, were asked to volunteer for this study. A total of 1095 men volunteered, but exclusions and dropouts during the preliminary phases reduced this number so that 846 men were ultimately randomised. Of these, 422 received the conventional control diet, and 424 the experimental diet.

The composition of the two diets is shown in table I. Food was served *ad libitum*, cafeteria style. Many of the subjects were in the Center only intermittently, and adherence to the diets was therefore monitored in terms of dining-room attendance records.

TABLE I—COMPOSITION OF DIETS

—	Control	Experimental
Fat calories (% of total)*	40·1 ± 2·2	38·9 ± 1·9
Iodine value of fat*	53·5 ± 3·5	102·4 ± 4·6
Linoleic acid (% of total fatty acid)† ..	10·0	38·4
Cholesterol (mg. per day)†	652·7	365·4
β-sitosterol (mg. per day)†	3·3	215·0
Other sterols (mg. per day)†	3·3	48·4

* Mean ± S.D. of 412 to 427 one-week pooled collections.
† Mean of 19 analyses, each representing a 4–10-week pool, weighted as to length of collection period.

Volunteers were accepted into the study regardless of possible pre-existing atherosclerotic complications. For purposes of morbidity and mortality data, a subject was considered a participant from the day he was assigned to diet until termination of the trial or until death, regardless of possible absence from the Center or non-cooperation during the interval. Adherence over the entire period of the trial thus defined amounted to 56% of total possible meals for the control subjects and 49% for the experimental group.

Clinical follow-up was carried out on a double-blind basis. Men were re-examined annually and on the occasion of any admission to hospital. Some morbidity occurring outside the Center presumably escaped attention, but ascertainment of mortality through Veterans Administration records was

1. Ahrens, E. H., Insull, W., Blomstrand, R. *Lancet*, 1957, i, 943.
2. Keys, A., Anderson, J. T., Grande, F. *Metabolism*, 1965, **14**, 747.

TABLE II—CHANGES IN SERUM-CHOLESTEROL *

Months after start of diet	Ratio of observed serum-cholesterol level to subject's baseline level					
	Control			Experimental		
	N.	Mean	S.E.	N.	Mean	S.E.
12	236	1·043	0·010	214	0·889	0·009
24	181	1·022	0·012	163	0·894	0·010
36	155	0·969	0·012	128	0·844	0·010
48	126	0·942	0·013	105	0·813	0·013
60	101	0·930	0·014	80	0·813	0·014
72	85	0·934	0·016	65	0·821	0·022
84	64	0·937	0·017	45	0·781	0·019
96	24	0·861	0·020	15	0·816	0·032

* The table is abridged; determinations were made at 4-month intervals.

estimated to be 99% complete. The primary end-point was ischæmic heart-disease manifested by sudden death or by myocardial infarction. Cerebral infarction and several other secondary end-points were also recorded. These included amputation due to peripheral atherosclerosis, ruptured aortic aneurysm, and intestinal infarction. Necropsy was obtained in 65% of the deaths.

Metabolic observations on the participants have already been described.[3–7]

Serum-cholesterol was determined by the method of Abell et al.[8] Composition of diets was monitored by analysis of homogenised, pooled collections representing each week's meals. Methods of food analysis have been described.[9]

3. Tompkins, M. J., Dayton, S., Pearce, M. L. *J. Lab. clin. Med.* 1964, **64**, 763.
4. Dayton, S., Hashimoto, S., Rosenblum, D., Pearce, M. L. *ibid.* 1965, **65**, 739.
5. Dayton, S., Hashimoto, S., Pearce, M. L. *Circulation*, 1965, **32**, 911.
6. Dayton, S., Hashimoto, S., Dixon, W., Pearce, M. L. *J. Lipid Res.* 1965, **7**, 103.
7. Dayton, S., Hashimoto, S., Pearce, M. L. *ibid.* 1967, **8**, 508.
8. Abell, L. L., Levy, B. B., Brodie, B. B., Kendall, F. E. *J. biol. Chem.* 1952, **195**, 357.
9. Dayton, S., Pearce, M. L., Hashimoto, S., Fakler, L. J., Hiscock, E., Dixon, W. J. *New Engl. J. Med.* 1962, **266**, 1017.

TABLE III—PRIMARY AND SECONDARY END-POINTS

—	No. of fatal events*	No. of non-fatal events	No. of men
Definite myocardial infarction by E.C.G. only:			
Control	0	4	4
Experimental	0	9	9
Definite overt myocardial infarction:			
Control	23	24	40
Experimental	23	10	27
Sudden death due to ischæmic heart-disease:			
Control	27	..	27
Experimental	18	..	18
Definite cerebral infarction:			
Control	9	16	22
Experimental	3	10	13
Ruptured aneurysm:			
Control	5	0	5
Experimental	2	0	2
Amputation:			
Control	3	2	5
Experimental	0	7	5
Miscellaneous:			
Control	3	3	6
Experimental	2	1	1
Total:			
Control	70	49	96†
Experimental	48	36	66†
χ^2 on totals	4·45	..	6·63
P	< 0·05	..	0 01

* Cases in which the event was either the sole cause or a partial cause of death.
† Because some subjects had multiple events in these categories, this figure is smaller than that obtained by totalling the column.

Predefined diagnostic criteria for clinical events will be documented in detail in a future publication.

RESULTS

Changes in serum-cholesterol concentration are shown in table II. The mean difference between the experimental group and the control group amounted to 12·7% of the starting level, which was similar for the two groups (control 234 mg. per 100 ml.; experimental, 233 mg. per 100 ml.).

Total duration of the study for each individual depended on the time of entry. The maximum period was 100

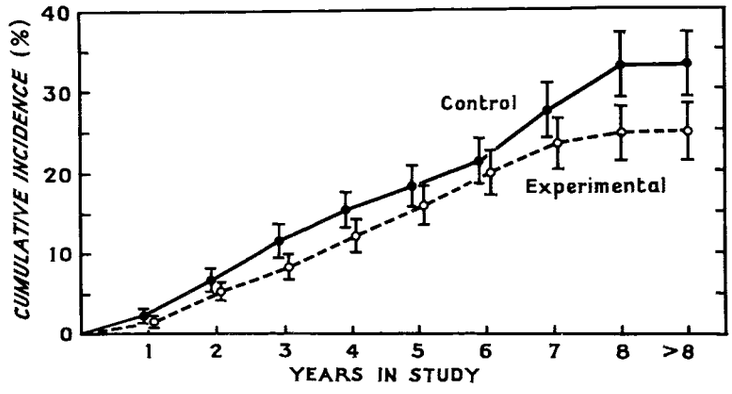

Fig. 1—Incidence curves for primary end-point (sudden death or definite myocardial infarction) computed by the life-table method.
Where a non-fatal myocardial infarction occurred, the participant was considered under follow-up only to the date of the event. Points are plotted as cumulative incidence-rates ± standard errors.

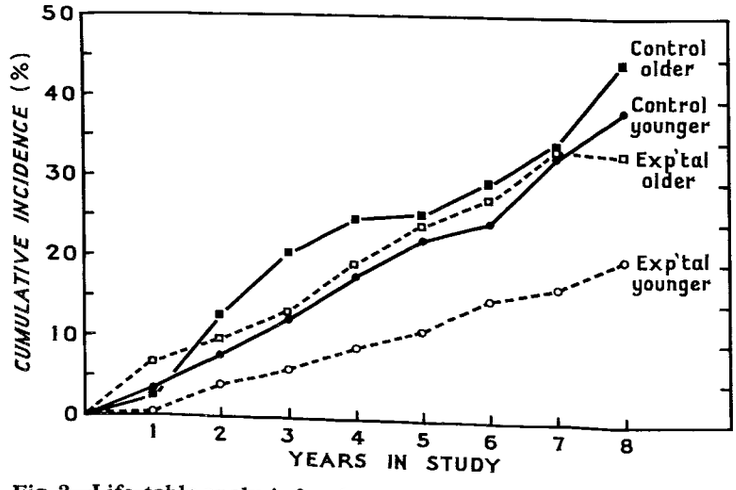

Fig. 2—Life-table analysis for the combined incidence of myocardial infarction, sudden death, and cerebral infarction.
In instances of non-fatal myocardial infarction or cerebral infarction, the subject was considered under follow-up only to the time of the event.

months. Table III presents summarised data on all events and fatalities in the various categories of primary and secondary end-points. Although sudden death and myocardial infarction were less common in the experimental group than among the controls, the difference was not significant. However, when these data are pooled with those for cerebral infarction or for all secondary end-points, significant differences emerge.

Fig. 1 shows combined incidence of sudden death and myocardial infarction analysed by the life-table method.[10] The P value for the difference between the two survival tables determined by the non-parametric method of Forsythe and Frey [11] is 0·48.

10. Cutler, S. J., Ederer, F. *J. chron. Dis.* 1958, **8**, 699.
11. Forsythe, A. B., Frey, H. S. Unpublished.

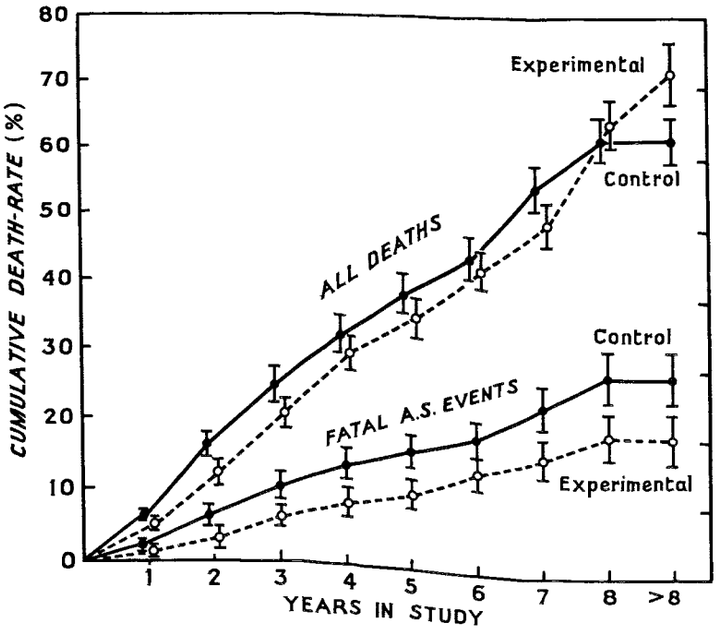

Fig. 3—Life-table analysis for deaths due to acute atherosclerotic events and for total mortality.

Points are plotted as cumulative death-rates ± standard errors.

Fig. 2 presents a life-table analysis of the pooled data for definite myocardial infarction, sudden death, and definite cerebral infarction, including stratification by age at entry into the study. The subjects were divided into two age strata of equal size, the cut point being 65·5 years. For both strata the incidence rates were lower for the experimental group than for the controls. For the older stratum this difference was not significant ($P=0·21$), whereas a P value of 0·06 was obtained for the younger stratum. For the combined data, unstratified by age, $P=0·04$.

Fatality data are shown in fig. 3. The incidence of fatal atherosclerotic events was lower in the experimental group than among the controls, but the P value for comparison was 0·26. There was little difference in total mortality rates (fig. 3). During the late part of the trial there was a crossover of the curves for total death-rates due to excess nonatherosclerotic mortality among the experimental subjects. In this phase of the trial, numbers were relatively small and the excess nonatherosclerotic mortality after the sixth anniversary amounted to 9 cases. The difference in nonatherosclerotic deaths in this period was due entirely to trauma (0 controls, 4 experimental) and to carcinoma (2 controls, 7 experimental).

In common with other tests of cholesterol-lowering diets, this trial had the disadvantages of relatively limited numbers of subjects and incomplete adherence to the dietary regimen. On the other hand, being a double-blind trial in randomised subjects it had the virtue of freedom from bias. The trial leads to the qualified conclusion that lowering of serum-cholesterol levels by the dietary means employed here can lower the incidence of atherosclerotic complications in men aged 54–65, but not necessarily at older age levels. The occurrence of some excess nonatherosclerotic mortality in the late stages of the trial raises a question, which we cannot yet answer, as to a possible toxic effect of the experimental diet.

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METHOD OF ASSESSING PROGNOSIS IN PATIENTS WITH MALIGNANT MELANOMA

Summary In a retrospective study of 161 patients with malignant melanoma, assessment of the combined influence of a number of features that seem to affect the outcome has been used as the basis of a semi-quantitative method of predicting the prognosis. In a prospective study of 54 patients, 45 (84%) fell into either the high-risk or low-risk group, for which the accuracy of prediction was nearly 90%, and the rest had intermediate scores, from which no useful prediction could be made.

INTRODUCTION

PREDICTION of prognosis for the patient with malignant disease is always difficult. This is especially true of patients with malignant melanoma apparently confined to the primary site at initial clinical and pathological assessment. This paper describes an attempt to devise a simple technique which would indicate the likely outcome for such patients.

PATIENTS AND METHODS

In 161 patients with histologically proven extraocular malignant melanoma seen at the Western Infirmary, Glasgow, between Jan. 1, 1952, and Dec. 31, 1961, and followed up to early 1967, the effects of numerous clinical and histopathological features on survival have been assessed and analysed statistically. This information is reported elsewhere.[1 2]

It became apparent from that study that no single factor, other than the presence of advanced disease as evidenced by spread to the regional or more distant lymph-nodes or by hæmatogenous dissemination, allowed an accurate forecast of likely outcome for the individual. It was, however, clear that several clinical and histological features had separately a minor influence on prognosis. It was postulated that by considering these features *in combination* a more valid estimate of prognosis might be made at a time when prognostication is otherwise largely guesswork.

Death-rates from melanoma in patients with and without each significant feature were compared, and an arbitrary

1. Cochran, A. J. *J. Path. Bact.* (in the press).
2. Cochran, A. J. *Cancer, N.Y.* (in the press).