CLIOQUINOL AND S.M.O.N.: REANALYSIS OF ORIGINAL DATA

SIR,—The epidemiological data on S.M.O.N. (subacute myelo-optic neuropathy) that seem to support the clioquinol hypothesis have been much debated.[1-5] Lee[1,2] and Meade[4] have refuted the clioquinol hypothesis after their own evaluation of these data. Arguing against Meade, Shigematsu[3] stressed that the second nationwide survey of clioquinol intake was inferior in accuracy to the first similar nationwide survey and that Meade should have cited the first survey.[5]

Dr R. Kono and Dr I. Shigematsu have kindly provided me with the original data of the first nationwide survey on the status of clioquinol intake by S.M.O.N. patients in Japan conducted by eighteen members of the clinical group of the S.M.O.N. Research Commission in September, 1970, to examine casual relationship between S.M.O.N. and clioquinol.[6] The data are questionnaires completed for 890 definite S.M.O.N. patients. These are the sole data collected after the clioquinol hypothesis, least prejudiced for the hypothesis, and evaluated by the Commission as the most reliable data.[5,7]

REANALYSED SURVEY DATA FOR EACH CLINICAL GROUP MEMBER

Name of member	No. of investigators	S.M.O.N. patients	No. of clioquinol non-takers	
			Before onset of abdominal symptoms	Within 6 mo before onset of neurological symptoms
Ofuji	4	47	32/43* *(74%)*	7/42* *(17%)*
Fujiwara	1	26	20/25 *(80%)*	0/26
Hayase	1	5	4/4	1/5
Ito	2	28	19/28 *(68%)*	0/28
Hiraki	22	43	30/36 *(83%)*	2/36 *(6%)*
Kuroiwa	2	32	26/29 *(90%)*	2/32 *(6%)*
Otsuka	2	2	2/2	0/2
Toyokura	4	60	45/51 *(88%)*	4/59 *(7%)*
Kosaka	2	34	30/31 *(97%)*	19/34 *(56%)*
Takasaki	1	31	15/15 *(100%)*	1/5
Tsubaki	1	39	12/20 *(60%)*	0/38
Miyoshi	11	24	19/21 *(90%)*	6/24 (25%)
Sugiyama	1	20	18/20 *(90%)*	7/19 *(37%)*
Ukyo	1	2	1/2	0/2
Sobue	1	199	121/196 *(62%)*	19/194 *(10%)*
Omura	1	234	127/155 *(82%)*	44/140 *(31%)*
Kusui	6	25	21/24 *(88%)*	1/24
Koshijima	11	39	27/33 *(82%)*	6/36 *(17%)*
Total	74	890	569/735	119/746

* Excluding patients whose history of drug intake or onset of symptoms was unclear in each group.

As defined by the Commission,[8] S.M.O.N. is a disease with abdominal disturbances as prodromal symptoms. In examining the hypothesis knowledge about clioquinol intake before onset of abdominal symptoms of S.M.O.N. is essential. My analysis revealed that 569 our of 735 S.M.O.N. patients whose history of drug intake was clear had never taken clioquinol before onset of S.M.O.N. The percentages of such non-takers for each survey member are 60–100, and mostly 70–80%. This finding proves that clioquinol is not a cause of S.M.O.N., yet the Commission did not make this analysis.

Instead, the Commission singled out the onset of neurological symptoms for analysis of the same original data and reported that there were 610 (82·2%) clioquinol takers and 110 (14·8%) non-takers among 742 S.M.O.N. patients[5] (119 definite non-takers among 746 patients according to my reanalysis). However, these percentage figures cannot be used to estimate ratios of clioquinol takers and non-takers among all S.M.O.N. patients. Because, the survey data were not collected on a random basis and because the material reported by survey members was widely diverse (e.g., the numbers of investigators engaged in the survey ranged from 1 to 22, reported cases varied from 2 to 234, and the frequency of clioquinol non-takers within six months before onset of neurological symptoms ranged from 0% to 55·9%). Even if such defects in the Commission's survey and analysis were set aside, the existence of 110 definite non-takers cannot affirm the causal relationship.

The data reported by two members were considered to be useful for statistical analysis of dose-response relationship. From the analysis of these data, no dose-response relationship was observed.

The original data of the first nationwide survey indicated that clioquinol is not a cause of S.M.O.N. The original data of the second survey should also be reanalysed, though my request for this material has been refused.

Department of Data Processing & Analysis,
Tanabe Seiyaku Co. Ltd.,
Osaka 541, Japan

MASASHI ASAO

**This letter has been shown to Dr Shigematsu, whose reply follows.—ED. L.

SIR,—Although Mr Asao claims to have reanalysed the data on clioquinol intake by S.M.O.N. patients, nothing is added to the results published by the S.M.O.N. Research Commission[1] from which the above data are derived. The Commission has never drawn any conclusion from these data with respect to the causal relationship between S.M.O.N. and clioquinol. Asao makes a mistake in tabulating the number of clioquinol non-takers before onset of abdominal symptoms which inevitably include both symptoms attributable to clioquinol and those of the primary disease which led to the intake of the drug.

Department of Epidemiology,
Institute of Public Health,
Tokyo 108, Japan

I. SHIGEMATSU
Chairman, S.M.O.N. Research Committee

LIPID PROFILES IN DIOXIN-EXPOSED WORKERS

SIR,—γ-glutamyl transpeptidase (G.G.T.), triglyceride, cholesterol, and high-density-lipoprotein (H.D.L.) cholesterol estimations were done on eight men with chloracne due to occupational exposure to the polychlorinated biphenyl 2,3,7,8-tetrachlorodibenzoparadioxin (T.C.D.D., dioxin). Some of the men had clinical signs of ischæmic vascular disease (table I). Five men had raised triglyceride and G.G.T. levels,

TABLE I—CLINICAL DETAILS AND LABORATORY TRENDS IN 8 MEN WITH CHLORACNE

No.	Age	Clinical details	Lipid results
1	44	Probable migraine; possible transient ischæmic attacks	Abnormal
2	44	Chloracne only	Abnormal
3	28	Chloracne only	Abnormal
4	29	Chloracne only	Normal
5	31	Arcus senilis	Abnormal
6	37	Chloracne only	Normal
7	61	Myocardial infarction	Abnormal
8	47	Myocardial infarction	Abnormal

1. Lee, J. A. H. *Lancet*, 1978, ii, 738.
2. Lee, J. A. H. *ibid.* p. 1108.
3. Shigematsu, I., Yanagawa, H. *ibid* p. 945.
4. Meade, T. W. *Br. J. prev. soc. Med.* 1975, **29**, 157.
5. Shigematsu, I. *Japan J. med. Sci. Biol.* 1975, **28**, 35.
6. Kusui, K. *ibid.* 1975, **28**, 57.
7. Yamamoto, S. *in* Epidemiological Issues in Reported Drug-induced Illnesses-S.M.O.N. and Other Examples (edited by M. Gent and I. Shigematsu); p. 172. Ontario, 1978.
8. Kono, R. *Japan. J. med. Sci. Biol.* 1975, **28**, 1.

1. Kusui, K., Shigematsu, I. Report of S.M.O.N. Research Commission no. 2, p. 226. 1971.

TABLE II—MEAN AND RANGE OF SERUM CONSTITUENTS IN LABORATORY CONTROLS AND IN MEN WITH CHLORACNE

Test*	Laboratory controls (n=100; age range 22–63)		Dioxin exposed (n=8; age range 28–61)
	Mean	Normal range†	Mean (and range)
G.G.T. (U/l)	24	up to 34	37 (14–57)
Triglyceride (mmol/l)	1·4	0·8–2·0	2·4 (1·2–3·7)
Cholesterol (mmol/)	5·7	3·8–7·6	6·5 (5·8–8·0)
H.D.L.-cholesterol (mmol/l)	1·25	0·81–1·69	1·06 (0·8–1·20)

*G.G.T by Szasz method (37°C); triglyceride and cholesterol by enzymatic methods; H.D.L. cholesterol by $MnCl_2$/heparin precipitation method.
†The laboratory controls were selected from hospital personnel to give a cross-section of social classes. Range is mean + and − 2 S.D.

and the other three had normal triglyceride and G.G.T. levels. All men had H.D.L. cholesterols below the method mean, total cholesterols above the method mean, and total/H.D.L.-cholesterol ratios consistent with a higher than average risk of ischæmic vascular disease. Laboratory results are summarised in table II.

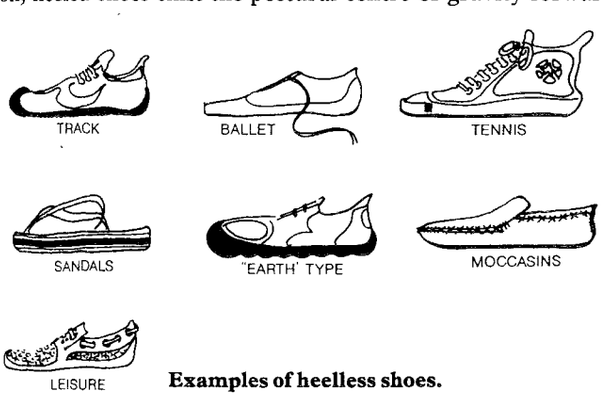
Dioxin is a potent enzyme inducer; lipid abnormalities, raised G.G.T. activities, and predisposition to ischæmic vascular disease have been separately recorded in dioxin-exposed subjects.[1] We suggest that, as in other clinical situations described by us,[2,3] the association of increased G.G.T. activity with abnormal lipid levels is due to enzyme induction, for which dioxin and/or other enzyme inducers could be responsible.

Departments of Dermatology and Chemical Pathology, Royal Hospital, Chesterfield S41 7SP

ANNE E. WALKER
JENNIFER V. MARTIN

FEET ON THE GROUND

SIR,—You note that platform shoes can cause bilateral hæmorrhages of the great-toe nails (Dec. 23 & 30, p. 1352). Moreover, heeled shoes put excess weight on the toes, causing a tendency for great toe and small toe to meet. Chronic exposure to high-heeled, pointed shoes causes this deformity and bunions to be common in our adult women patients. In addition, heeled shoes shift the postural centre of gravity forward,



Examples of heelless shoes.

resulting, in the experience of orthopædic surgeons at the Kaiser-Permanente Medical Center, in exaggerated lumbar lordosis, compensatory kyphosis, protuberant abdomen and buttocks, and low back pain, a chronic posterior-facet syndrome.

1 World Health Organisation. Monograph on Chlorinated Dibenzodioxins. August, 1977.
2 Martin, P. J., Martin, J. V., Goldberg, D M. *Br. med. J.* 1975, i, 17.
3 Martin, J. V., Martin, P. J., Goldberg, D. M. *Lancet*, 1976, i, 7.

Furthermore, instability of walking stance associated with heeled shoes results in numerous falls with hip fractures. Since inpatients with hip fractures sometimes die of pneumonia, heeled shoes can kill as well as injure and deform. Perhaps doctors should be recommending heelless shoes (figure). Fortunately, some elderly southern California women wear tennis shoes, a sensible practice adopted quite late in life. Moreover, observation of children at play indicates that shoeless ones seldom fall whereas shod ones fall frequently. Is it, therefore, possible that we should also be recommending barefootedness when practical? Feminists have burned their bras; perhaps they should burn their high-heeled shoes as well.

Kaiser-Permanent Medical Center, Los Angeles, California 90027, U.S.A.
JOHN M. DOUGLASS
SUE N. DOUGLASS

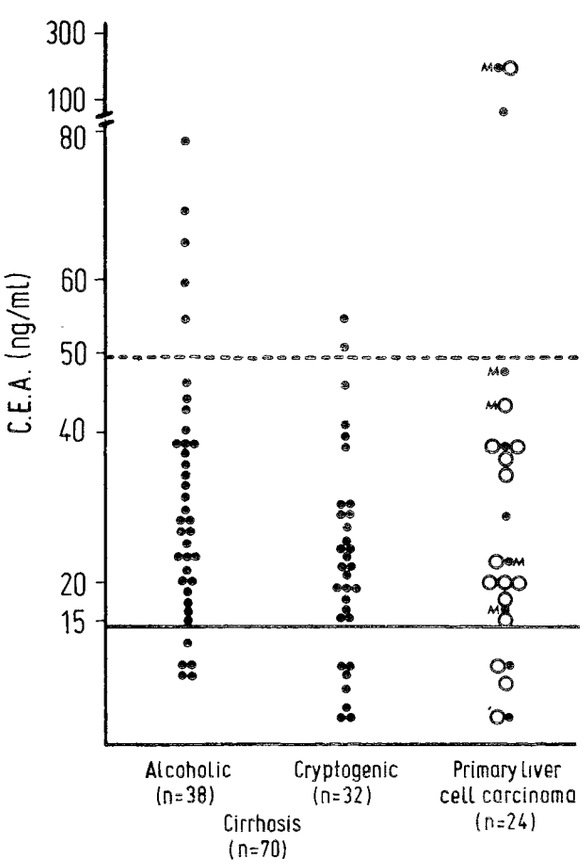
U. S. C. School of Medicine and Kaiser-Permanente Medical Center, Los Angeles
IRVING M. RASGON

U.C.L.A. School of Medicine, Los Angeles, California
PAUL M. FLEISS

CARCINOEMBRYONIC ANTIGEN IN LIVER DISEASE

SIR,—Dr Hine and co-workers[1] suggest the possible value of carcinoembryonic antigen (C.E.A.) determination in malignant liver disease. We have been using C.E.A. assay on 70 patients with cirrhosis of the liver (alcoholic and non-alcoholic) and on 24 patients with primary liver-cell cancer (P.L.C.C.); all were diagnosed by liver biopsy. We use a double-antibody radioimmunoassay[2] (upper limit of normal 15 ng/ml). Our results are shown in the figure. In 81% of patients with cirrhosis and 79%

1. Hine, K. R., Leonard, T. C., Booth, S. N., Dykes, D. W. *Lancet*, 1978, ii, 1337.
2. Egan, M. L., Lautenschleger, J. T., Coligan, J. E., Todd, C. W *Immunochemistry*, 1972, **9**, 289.



C.E.A. in cirrhosis and P.L.C.C.
O=carcinoma+cirrhosis; M=extrahepatic metastasis.