The response to vitamin D also varied with the initial concentrations of 25-OHD. When subjects were divided into groups with 25-OHD concentrations below and above 20 (8 ng/ml), 25-OHD concentrations rose steeply in those with low initial concentrations, while subjects starting with higher values showed only marginal changes. These findings support the view that vitamin D hydroxylation is regulated by product inhibition.⁵ Once physiological levels of 25-OHD are reached further vitamin D is less likely to be converted into active metabolites.

Consideration should be given to the dose of vitamin D necessary to correct deficiency in patients with low 25-OHD levels. Two months after the start of treatment with 500 IU of vitamin D elderly subjects with initial 25-OHD concentrations of under 20 nmol/l (8 ng/ml) had a mean 25-OHD concentration of 52.5 nmol/l (21 ng/ml) with 95% confidence limits of 26.3 to 104.7 nmol/l (10.5 to 41.9 ng/ml). These values are almost identical to the 95% confidence limits of 25 to 100 nmol/l (10 to 40 ng/ml) found in healthy young adults.⁶ It would thus appear that on a regular daily dose of 500 IU of vitamin D most old people would avoid the dangers of vitamin D deficiency.

The response of subjects to 2000 IU of vitamin D daily over one month was greater than that recorded for those on 500 IU in July but almost identical to that found for those on 500 IU in November. This further illustrates the difficulties of comparing 25-OHD concentrations in samples taken at different times. It is more valid to note that in February the mean 25-OHD concentrations of subjects on 500 IU of vitamin D daily for

four months and those on 2000 IU daily for six months were 52.5 nmol/l and 81.3 nmol/l (21.2 and 32.5 ng/ml) respectively. Thus a fourfold increase in dosage over a longer period of time had produced only a marginally higher blood concentration. This is further evidence of 25-OHD concentrations being controlled by feedback regulation.

A daily dose of 500 IU of vitamin D seems to produce adequate concentrations of 25-OHD in most old people. The use of larger doses in conditions other than renal disease, malabsorption, or overt metabolic bone disease does not seem justified. A large-scale study is now required to assess whether controlling 25-OHD concentrations would have any effect on the incidence and consequences of metabolic bone disease in old age.

References

- Anderson, I, *et al*, *Scottish Medical Journal*, 1966, **11**, 429.
- Chalmers, J, *et al*, *Journal of Bone and Joint Surgery*, 1967, **49B**, 403.
- Corless, D, *et al*, *Lancet*, 1975, **1**, 1404.
- Nayal, A S, *et al*, submitted for publication.
- Belsey, R E, De Luca, H F, and Potts, J T, *Journal of Clinical Endocrinology and Metabolism*, 1974, **38**, 1046.
- Stamp, T C B, and Round, J M, *Nature*, 1974, **247**, 563.
- McLaughlin, M, *et al*, *Lancet*, 1974, **1**, 536.
- Haddad, J G, and Stamp, T C B, *American Journal of Medicine*, 1974, **57**, 57.

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CONDENSED REPORT

Treatment of borderline diabetes: controlled trial using carbohydrate restriction and phenformin

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Summary

A five-year therapeutic trial of carbohydrate restriction with or without phenformin (50 mg/day) was performed in men with borderline diabetes. The aim of treatment was to diminish the enhanced risk of cardiovascular disease and deterioration of glucose tolerance. Cardiovascular morbidity and mortality were not significantly affected by any form of treatment, alone or in combination. The predominant risk factor for cardiovascular morbidity and mortality and for overall mortality was the initial blood pressure level. The baseline plasma cholesterol concentration significantly predicted the onset of intermittent claudication.

One implication of the results is that hypotensive

treatment, supplemented when necessary with hypolipidaemic treatment, may be more effective in preventing the progression of arterial disease in people with mild to moderate glucose intolerance than conventional antidiabetic therapy.

Introduction

People with slightly impaired glucose tolerance, whether or not diagnosed formally as diabetic, have an increased risk of developing a more manifest diabetes—with fasting hyperglycaemia¹—and coronary heart disease.² Such “borderline diabetics” thus constitute a high-risk group in whom the influence of treatment on metabolic and vascular phenomena can be systematically and ethically studied. Previous studies have suggested that sulphonylurea treatment might be beneficial,³⁻⁵ but the differences from placebo-treated controls have not been large and any conclusions must be guarded. The large population of male civil servants submitted to systematic blood sugar and cardiovascular screening in 1968-70⁶ provided us with the opportunity to identify a new group of borderline diabetics and examine the effects of treatment in a rather more homogeneous population than in our previous study in Bedford.

The basic design of the study was to compare the effects of advice to restrict carbohydrate consumption to 120 g/day with advice simply to reduce sucrose intake. Within each of these two diet groups the effect of treatment with a low dose of phenformin

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(50 mg sustained-release preparation daily) was compared with that with an identical placebo capsule. Phenformin was selected because of reports that, in addition to its effects on blood glucose, it might be expected to be valuable in preventing arterial disease by lowering plasma lipid levels⁶ and stimulating plasma fibrinolytic activity.⁷

Patients and methods

Almost all of the subjects for the trial were recruited between 1968 and 1970 from the Whitehall survey, a screening survey of male civil servants working in London, described in detail by Reid *et al.*⁵ A few were recruited from the pilot phase of the Whitehall survey, which was carried out, using the same screening techniques, among Post Office employees.

The survey procedures included a measurement of the capillary, whole-blood sugar concentration two hours after a 50-g glucose load (235 ml liquid glucose BP as Lucozade Beechams, Ltd), using the Hoffman ferricyanide method adapted to the Technicon Autoanalyser (Technicon method N-9a). The drink was taken in the morning after an overnight fast. Men with blood sugar concentrations of 6.1 to 11.0 mmol/l (110 to 199 mg/100 ml) were recalled for a standard 50-g oral glucose tolerance test (GTT), which was performed in the afternoon, beginning at about 1500, after the men had fasted from 0800. Men with two-hour blood sugar concentrations of 11.1 mmol/l (200 mg/100 ml) or more at the survey examination or during the GTT were referred directly to their general practitioner as probable diabetics. Men were classified as borderline diabetics if they had (a) a survey blood sugar concentration of 6.1 to 11.0 mmol/l (110-199 mg/100 ml); or (b) a peak blood sugar concentration of >10.0 mmol/l (180 mg/100 ml) and a two-hour blood sugar concentration of 6.7-11.0 mmol/l (120-199 mg/100 ml) in the GTT; or two values exceeding 10.0 (180 mg/100 ml) in the GTT; or a mean two-hour blood sugar value (survey and GTT) of >6.7 mmol/l (120 mg/100 ml), or a combination of these.

We explained to the men who fulfilled these criteria that although they had impaired glucose tolerance, they were not diabetic in the usual (diagnostic) sense of the word, and that there was no consensus whether treatment was necessary or not, nor what treatment should be. We further explained that, if they agreed, we proposed to observe them at regular intervals over several years, comparing the effects of dietary and drug treatment among them. Of those eligible for the trial 95% agreed to participate. Before final recruitment a description of the purposes and procedures of the trial and of the findings in each potential subject for the study was sent, with the individual's consent, to his general practitioner, who was invited to submit any observations, questions, or reservations about his patient's participation. Several doctors made pertinent observations or queries, but none objected to participation.

TRIAL DESIGN

At the first visit to the special research clinic subjects were allocated at random to one of four treatment groups: (a) they were recommended to take 120-g carbohydrate diet plus given placebo capsules; (b) they were recommended to "limit sucrose—that is, table sugar—intake" and given placebo capsules; (c) they were recommended to take 120-g carbohydrate diet plus given 50 mg phenformin once daily; (d) they were recommended to "limit sucrose intake" and given 50 mg phenformin once daily.

Those recommended to take a restricted carbohydrate diet were given careful verbal instructions and a specially prepared booklet along the lines of the 10-g portion diet, used in the UK for instructing diabetics about diet.* No recommendations were made about non-carbohydrate foods. The diet part of the trial was not "blind." Previous experience with the Bedford borderline trial led us to conclude that dietary advice should be reiterated periodically. The drug trial was planned to run for the first five years of the study and to be "double-blind." Phenformin and placebo capsules looked alike and were dispensed by an assistant from records kept separately from the subjects' folders. After the first visit, subsequent examinations were made about every six months.

Before the trial began we decided that severe or sustained worsening of glucose tolerance would be a main reason for withdrawing a person from the trial, though observation would be continued. The criteria

used for determining this "worsening to diabetes" were: (a) two-hour blood sugar concentrations of 11.1 mmol/l (200 mg/100 ml) or more at two successive visits to the research clinic; (b) three non-successive two-hour blood sugar concentrations of 11.1 mmol/l (200 mg/100 ml) or more; (c) the development of unequivocal symptoms or signs of diabetes mellitus, irrespective of the blood sugar level. If any of these occurred, the subject was informed and promptly referred to his general practitioner with the recommendation that he be regarded as a diabetic and receive conventional clinical care.

At the first trial visit venous blood was taken, after an 8-10 hour fast, for measuring cholesterol and triglycerides. Cholesterol was measured on an Autoanalyser by the method of Levine and Zak⁸ and triglycerides were measured by the fluorimetric method of Cramp and Robertson.⁹ Electrocardiography (ECG; limb leads only) was performed at the survey and subsequently at the 5th and 10th visits, using a Minograph 31B and "multipoint" electrodes. All records for men in the trial were coded independently by the same two observers using the Minnesota code.¹⁰ When they disagreed a third person adjudicated. The final Minnesota codes were grouped into three categories, indicating the likelihood of cardiac ischaemia. Codes 1:3, 4:1, 4:2, 4:3, 5:1, 5:2, and 5:3 indicated possible ischaemia (category 1); codes 1:1, 1:2, and 7:1 indicated probable ischaemia (category 2); and any other code indicated no ischaemia (category 0). Blood pressure was measured in the right arm in the sitting position at each clinic visit except the fourth. At each visit the men were asked about any ill-health over the preceding six months and specifically (and systematically) about symptoms of angina, myocardial infarction, intermittent claudication, or stroke. When appropriate further information was sought from general practitioners or hospitals concerned in diagnosis or treatment. A list of available baseline data is given in table A.*

ANALYSIS

This report is concerned with information collected up to and including the 10th trial visit—that is, up to five years after entry into the trial. At this time phenformin and placebo capsules were discontinued, though the dietary trial continues and observation will continue for up to 10 years. We have concentrated here on cardiovascular morbidity and mortality, and this has been analysed in terms of the following "endpoints."

Angina pectoris—The appearance of angina during the follow-up period counted as a single event, even if it subsequently disappeared and reappeared. People with a history of angina at entry into the trial could not, by this definition, qualify for new angina subsequently.

Myocardial infarction—A diagnosis of myocardial infarction was accepted either on the basis of the World Health Organisation (WHO) questionnaire¹¹ or when a firm diagnosis had been made by an attending doctor in general practice or hospital. People entering the trial with a history of myocardial infarction qualified for a new event if a further infarction occurred.

Intermittent claudication—This was assessed by the WHO questionnaire. As with angina, only the first presentation of the symptom was counted.

Stroke—This included the various clinical manifestations of cerebrovascular disease including subarachnoid haemorrhage.

ECG change—A change of Minnesota code category from no to possible or probable ischaemia (0 to 1 or 2) or from possible to probable ischaemia (1 to 2) was counted as a single event. If an individual experienced two changes, from survey to 5th visit and from 5th to 10th visit this was still counted as a single event.

Death—Deaths of all survey participants, including those in our trial, were notified by the National Health Service Central Registry. Copies of death certificates and of necropsy reports were obtained. The cause of death as stated on the certificate was accepted. Sudden death and death from myocardial infarction (or coronary thrombosis), heart failure, or hypertensive heart disease (ICD codes 400-404, 410-414, 420-429) were combined for some parts of the analysis in a category of cardiovascular death.

When these endpoints were related to treatment we assumed, for the purposes of the analysis, that the individual continued for the whole of the trial with the treatment initially allocated. Of course, changes did occur for several reasons. Some men developed diabetes by the criteria outlined above (see table 1). In others treatment with capsules was stopped because of side effects. Several admitted to defaulting from treatment and a few defaulted entirely from the study. Although we attempted to monitor adherence to capsule treatment, the assess-

*Copies are available on request.

*Copies of tables A-F are available from the authors.

ment was inevitably fairly crude. Some men who were recommended to take a 120-g carbohydrate diet did not follow the advice and others, advised to take a low-sucrose regimen, lost a large amount of weight, presumably as a result of self-imposed restrictions.

Results and comment

PREDICTIVE POWER OF BASELINE VARIABLES

Several baseline measurements made at visit 1, at which treatment was allocated, are presented in tables I and B. The randomisation procedure was not entirely successful and several variables differed significantly between groups. Though regrettable, it can be allowed for by suitable statistical methods and has not affected our conclusions. We evaluated the relation between baseline measurements and cardiovascular event rates by calculating event rates in each quintile of distribution of five putative risk factors—systolic blood pressure, plasma cholesterol concentration, plasma triglyceride concentration, two-hour blood sugar concentration, and degree of obesity (expressed as the body mass index (BMI):weight/height²). The results are presented in fig 1 for the endpoints ECG change, angina, myocardial infarction, a combination of coronary events (ECG change, angina, infarction, or coronary death, or combinations of two or more), and death from any cause. Only for blood pressure was there a systematic relation between event rate and ascending quintile of baseline level.

FIG 1—Event rates for five endpoints (see text) in relation to quintiles of distribution at baseline of systolic blood pressure, plasma cholesterol, BMI, plasma triglyceride, and two-hour blood sugar in the glucose tolerance test.

There was no systematic relation between cholesterol level and event rate, though the highest quintile appeared to contribute an excess proportion of myocardial infarctions and deaths. There was also no evidence of an effect of cigarette smoking (table C) or of heart rate on morbidity or mortality.

The relation between baseline risk-factors and cardiovascular event rates was further examined using the multiple logistic model¹² with the following independent variables: age; systolic blood pressure;

cholesterol concentration; log₁₀ (triglyceride concentration); blood sugar (two-hour level in GTT); BMI; current cigarette smoking (dummy variable); carbohydrate restriction (dummy variable); phenformin treatment (dummy variable).

The purpose of these analyses was twofold. We hoped to find which baseline variables were most important in predicting the occurrence of a given event and to determine whether or not estimated treatment effects could have been obscured or enlarged by baseline differences between the treatment groups.

The results of the analysis were, however, rather disappointing. Perhaps because of the small sample size, no more than one variable achieved statistical significance for any event and, although this in itself was not surprising, the estimated coefficients were also generally small and in some cases even negative. Variables were excluded from the regression equation and re-entered later according to the size of their coefficients, but conclusions were unaltered and in general agreed with the earlier quintile analysis.

For each of the events ECG change, angina, myocardial infarction, and death the single most predictive risk factor was blood pressure; cholesterol was the only statistically significant predictor of claudication, and with only eight cases of stroke (out of 163 with complete baseline data and follow-up information) it was rather optimistic to expect the logistic model to provide significant relations. While these results do not provide much further information than the simpler univariate methods of quintile analysis they emphasise again the importance of blood pressure as the major risk-factor in this group.

The results of one analysis for predicting the most common event, ECG change, are presented in table II. Apart from blood pressure, only the coefficient for phenformin approached significance, reflecting the treatment difference expressed in table D (26.7% of the placebo group compared with 17.0% of the phenformin group had an ECG change).

TABLE II—Multiple logistic model: prediction of ECG change

Variable	Coefficient	Standard error	t	Mean values (±SD)	
				ECG change (n=37)	No ECG change (n=133)
Age (years)	0.025	0.032	0.78	58.8 ± 6.5	55.7 ± 7.3
Systolic blood pressure (mm Hg)	0.035	0.009	3.92	160.1 ± 30.3	137.0 ± 22.8
Cholesterol (mmol/l)	0.077	0.193	0.50	5.72 ± 1.39	5.60 ± 1.21
Log ₁₀ (triglyceride) (mmol/l)	-24.32	20.27	-1.20	0.134 ± 0.19	0.143 ± 0.20
2-hour blood sugar (mmol/l)	0.108	0.126	0.87	8.35 ± 1.34	8.22 ± 1.71
BMI	-0.013	0.066	-0.19	26.4 ± 3.7	26.1 ± 3.4
Smoking	0.156	0.435	0.36	43.2%*	42.1%
On diet	-0.414	0.432	-0.96	45.9%	48.9%
On phenformin	-0.840	0.455	-1.84	40.5%	54.9%

*Percent of group total smoking, on diet, on phenformin. Conversion: SI to traditional units—Blood sugar: 1 mmol ≈ 18 mg/100 ml.

EFFECTS OF TREATMENT ON WEIGHT

The mean weight at each visit for men attending all clinics is shown by treatment groups in fig 2. Subjects assigned to carbohydrate restriction began with a higher mean weight, which fell significantly between visits 1 and 2 and remained at this level throughout the trial. There was a much smaller decrease in the mean weight of the sucrose-restricted group. There was no significant effect of phenformin over placebo discernible in either diet group.

TABLE I—Mean baseline values (±SD) according to treatment group. Numbers of patients are given in parentheses

	No diet	Diet	Placebo	Phenformin	Total
Blood pressure (mm Hg)					
Systolic	138.8 ± 26.0 (106)	146.3 ± 26.5 (98)*	143.2 ± 24.0 (98)	141.7 ± 28.6 (106)	142.4 ± 26.4 (204)
Diastolic	85.8 ± 13.1 (106)	90.5 ± 14.8 (98)†	87.9 ± 13.8 (98)	88.1 ± 14.4 (106)	88.0 ± 14.1 (204)
Cholesterol (mmol/l)	5.58 ± 1.11 (100)	5.69 ± 1.24 (97)	5.85 ± 1.20 (97)	5.42 ± 1.12 (100)§	5.63 ± 1.18 (197)
Triglyceride (mmol/l)	1.37 ± 0.84 (106)	1.62 ± 0.70 (98)†	1.70 ± 0.82 (98)	1.30 ± 0.70 (106)‡	1.49 ± 0.79 (204)
Weight (kg)	74.9 ± 11.8 (105)	79.5 ± 11.5 (98)†	77.8 ± 12.6 (97)	76.5 ± 11.1 (106)	77.1 ± 11.8 (203)
BMI	25.3 ± 3.4 (104)	27.2 ± 3.4 (93)‡	26.4 ± 3.7 (93)	26.0 ± 3.4 (104)	26.2 ± 3.5 (197)

Diet v no diet: *P<0.05; †P<0.02; ‡P<0.001. Placebo v phenformin: §P<0.02; ‡P<0.001. Conversion: SI to traditional units—Cholesterol: 1 mmol/l ≈ 38.6 mg/100 ml. Triglyceride: 1 mmol/l ≈ 88.5 mg/100 ml.

FIG 2—Mean weight in kilograms for a cohort of men attending every follow-up visit according to treatment: placebo compared with phenformin, and recommended diet compared with sucrose restriction.

EFFECTS OF TREATMENT ON BLOOD PRESSURE AND PULSE RATE

In the University Group Diabetes Program (UGDP) trial with phenformin¹³ a rise in blood pressure and pulse rate was observed shortly after treatment had begun, and both systolic and diastolic pressure increased progressively throughout the trial. We calculated heart rates from the ECGs recorded at baseline and at the 5th visit, when subjects took their capsules up to and including the day of the clinic visit (table D). A significant fall in heart rate occurred in the restricted carbohydrate group, who had a higher rate at the survey examination. The fall was similar whether phenformin or placebo accompanied the diet. In no group was there evidence of an effect of phenformin on heart rate, nor did phenformin have observable effects upon blood pressure behaviour compared with placebo (fig 3). A detailed analysis of blood pressure changes in relation to treatment will be presented later.

FIG 3—Mean systolic blood pressure for a cohort of men attending every follow-up visit according to treatment: phenformin compared with placebo.

EFFECTS OF TREATMENT ON GLUCOSE TOLERANCE

The number of people whose condition worsened to diabetes by the criteria detailed earlier is shown in table III. The smallest number occurred in the group assigned to phenformin and carbohydrate restriction, but differences between the treatment groups were not statistically significant. A detailed analysis of blood sugar behaviour in relation to treatment will be presented later.

TABLE III—Proportion* of patients in each group whose condition worsened to diabetes

	Placebo	Phenformin
Sucrose restriction	45 (11.1%)	49 (6.1%)
Recommended diet	44 (4.5%)	43 (2.3%)

*Percentages are based on those with complete data on glucose tolerance up to and including ninth visit.

EFFECTS OF TREATMENT ON CARDIOVASCULAR EVENTS

The details are presented in tables E and F. No individual treatment or combination of treatments significantly affected any event or group of events.

ADHERENCE TO TREATMENT

Since some patients did not adhere completely to their assigned treatment, the total death rates and rates of death from cardiovascular causes were adjusted by the relative allocation method.¹⁴

A patient was defined as taking placebo or phenformin for a given six-month period provided he missed fewer than 50 capsules during that time. Otherwise he was assumed to have been on no treatment for that cycle. Thus a typical patient having taken (say) phenformin for seven cycles out of 10 was assigned seven-tenths to phenformin and three-tenths to no treatment. This method led therefore to an extra treatment group—no treatment—and the effective number of individuals in each group was no longer necessarily a whole number.

The results are presented in table IV. Although the total death rate in the placebo group was somewhat reduced by the method, there remained no significant differences between groups after allowing for different rates of adherence.

TABLE IV—Relative allocation method: adjustment of death rates for adherence to assigned treatment

	Crude death rate (%)	Relative allocation death rate (%)	Effective No of observations
<i>All deaths</i>			
Phenformin	6.6	6.1	78.7
Placebo	6.1	3.4	79.6
No treatment		9.8	45.7
<i>Deaths from cardiovascular causes</i>			
Phenformin	5.7	6.1	78.7
Placebo	4.1	3.1	79.6
No treatment		5.8	45.7

Discussion

The clinical importance of mild glucose intolerance (or borderline diabetes) lies in the increased risk of arterial disease and of progression to subsequent florid diabetes. We attempted to evaluate the effects on these risks of two kinds of treatment widely used in diabetes—weight reduction by carbohydrate restriction, and a pharmacological approach with the oral antidiabetic agent phenformin. Treatment with phenformin offered the theoretical advantages of beneficial effects on blood sugar, plasma lipids, and fibrinolysis.^{6,7} Since the study began, however, the UGDP have reported the results of their trial of phenformin in the treatment of maturity onset diabetes. In their study¹³ the mortality in the patients treated with phenformin (100 mg/day) was significantly greater than that in the combined groups treated with insulin or with a placebo tablet. Furthermore, the phenformin-treated patients showed a mean increase in both blood pressure and pulse rate which became obvious shortly after the start of treatment. In our own study none of these apparent effects of phenformin occurred. Whether the discrepancy between the two studies is due to differences in the subjects studied, the different doses of phenformin, or to chance can only be hypothesised.

We could find no effects, beneficial or otherwise, of either

form of treatment on cardiovascular morbidity and mortality. Although disappointing, this is not altogether surprising in view of the overwhelming preponderance of the blood pressure level as the major risk factor for cardiovascular morbidity and mortality in this group. Some workers have found that the blood pressure is a more significant risk factor for arterial disease among established diabetics than among non-diabetics.¹⁵ Possibly hypotensive treatment should therefore be more readily used in people who also have glucose intolerance or diabetes. The only other conventional risk factor which also had some predictive power in borderline diabetics was the plasma cholesterol concentration. The implication of this finding is that diets aimed at lowering plasma cholesterol might be more appropriate than simply low-carbohydrate or low-calorie diets, as we have discussed more fully elsewhere.²

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Copies of the unpublished tables can be obtained from Dr R J Jarrett, Unit for Metabolic Medicine, Department of Medicine, Guy's Hospital Medical School, London Bridge, London SE1 9RT.

References

- 1 Jarrett, R J, and Keen, H, *Lancet*, 1976, **2**, 1009.
- 2 Jarrett, R J, and Keen, H, *Complications of Diabetes*, ed H Keen and J Jarrett, p 179. London, Edward Arnold, 1975.
- 3 Keen, H, Jarrett, R J, and Fuller, J H, in *Proceedings of the 8th Congress of the International Diabetes Federation*, ed W J Malaisse and J Pirart, International Congress Series No 312, p 588. Amsterdam, Excerpta Medica, 1974.
- 4 Carlstrom, S, Persson, G, and Schersten, B, *Diabetes*, 1975, **24**, suppl No 2, p 414.
- 5 Reid, D D, *et al*, *Lancet*, 1974, **1**, 469.
- 6 Schwartz, M J, Mirsky, S, and Schaefer, L E, *Metabolism*, 1966, **15**, 808.
- 7 Fearnley, G R, *Postgraduate Medical Journal*, 1968, **44**, 468.
- 8 Levine, J, and Zak, B, *Clinica Chimica Acta*, 1964, **10**, 381.
- 9 Cramp, D G, and Robertson, G, *Analytical Biochemistry*, 1968, **25**, 246.
- 10 Blackburn, H, *et al*, *Circulation*, 1960, **21**, 1160.
- 11 Rose, G, and Blackburn, H, *Cardiovascular Survey Methods*, Monograph Series No 56. Geneva, WHO, 1968.
- 12 Walker, S H, and Duncan, D B, *Biometrika*, 1967, **54**, 167.
- 13 University Group Diabetes Program, *Diabetes*, 1975, **24**, Suppl No 1, p 65.
- 14 Report of the Committee for the Assessment of Biometric Aspects of Controlled Trials of Hypoglycemic Agents, *Journal of the American Medical Association*, 1975, **231**, 601.
- 15 Goodkin, G, *Journal of Occupational Medicine*, 1975, **17**, 716.

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SIDE EFFECTS

Perforation of chronic peptic ulcers after cimetidine

The H₂ receptor antagonist cimetidine has been marketed in Britain since November 1976 (as Tagamet). It has been generally acclaimed for its success in treating peptic ulceration, and there have been few reported side effects. We report here three cases of perforation of chronic peptic ulcers in which abrupt cessation of treatment with cimetidine may have precipitated the perforation.

Case 1

A 59-year-old man who had had symptoms of peptic ulcer for 25 years was admitted on 10 January 1977 with a perforated duodenal ulcer. He had not been investigated previously for his dyspepsia. Five days before his admission he had completed a six-week course of cimetidine, 200 mg thrice daily plus 400 mg at night (200 tablets), which had completely relieved his symptoms. At laparotomy a large perforation of a chronic duodenal ulcer with gross contamination of the peritoneal cavity was found and simple closure of the perforation was carried out.

Case 2

A 43-year-old man with a five-year history of symptoms of peptic ulcer was admitted on 13 June 1977 with a perforated gastric ulcer. A barium meal examination in 1973 had confirmed prepyloric ulceration. Ten days before admission he had completed a four-week course of cimetidine, 200 mg thrice daily plus 400 mg at night (140 tablets), which gave no symptomatic relief. Laparotomy showed that a 3-cm prepyloric ulcer crater had perforated with gross contamination of the peritoneal cavity. Simple closure of the perforation after biopsy was carried out. Biopsy confirmed a benign gastric ulcer.

Case 3

A 43-year-old woman who had had symptoms of peptic ulcer for 12 years was admitted on 13 June 1977 with a perforated duodenal ulcer. A barium meal examination in 1965 had shown deformity of the duodenal cap. Ten days before admission she had completed a six-week course of cimetidine, 200 mg thrice daily plus 400 mg at night (200 tablets), which had given complete relief of her symptoms. At laparotomy moderate contamination of the peri-

toneal cavity from a perforated duodenal ulcer was found, and a truncal vagotomy and pyloroplasty were carried out.

Comment

During the six months from December 1976 to June 1977 17 patients with perforated peptic ulcers (14 duodenal ulcers and three gastric ulcers) required laparotomy in this district hospital group. In the three patients described here acute perforation of a chronic ulcer had occurred within two weeks of an abrupt cessation of cimetidine treatment. This complication has not been described.

In reviewing published work on H₂ receptor antagonists we found one further case of perforation of a duodenal ulcer occurring six days after stopping metiamide,¹ the predecessor of cimetidine. In this case the patient had been given a one-month course of metiamide followed by 400 mg at night as a maintenance dose for eight months. The perforation occurred six days after the maintenance dose was stopped, and the patient died.

There are two disturbing features to highlight in our three cases. Firstly, all three patients were prescribed cimetidine by their general practitioners and had no pretreatment investigation and no subsequent investigation planned to confirm ulcer healing. The possibility of treating a gastric cancer was therefore not excluded, and cimetidine can produce symptomatic relief in gastric cancer.² Secondly, in all three patients the large size of the perforation resulted in moderate to gross contamination of the peritoneal cavity, which precluded definitive ulcer surgery in two of the patients.

The perforations may have occurred because of rebound hyperacidity after cimetidine had been stopped, but there is no consistent evidence of a "rebound" rise in gastric acid secretion in the studies so far carried out.^{3 4} Alternatively, the partially healed chronic ulcer which has responded to cimetidine may be less resistant to perforation when exposed to the normal acid concentrations after cimetidine has been stopped.

Conclusion—As a result of this experience we recommend that the treatment of a chronic peptic ulcer with cimetidine should be conducted as follows. An initial course, consisting of 200 mg thrice daily plus 400 mg at night, should last at least six weeks and be followed immediately by a maintenance course of 400 mg at night for three months or until ulcer healing has been shown on endoscopy. This treatment regimen should be considered even if there is no sympto-