FACTORS INFLUENCING THE BUTTERFAT-TOLERANCE TEST*

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Previous reports[1,2] have stressed the greater and more prolonged alimentary lipaemia in patients with ischaemic heart disease, following the administration of a test meal of 70 G. of butterfat. Neither the age nor the race of the candidates tested influenced the tolerance to the test meal. In this paper an examination has been made of those factors thought likely to influence the fat-tolerance test.

INDIVIDUALS STUDIED

Altogether, 219 males were fed a test meal containing 70 G. of butterfat. The subjects were divided into an outpatient group comprising 149 volunteers and an inpatient group of 70. Each group, in turn, was formed of test subjects with proved myocardial infarction and control subjects with no clinical or electrocardiographic evidence of heart disease. There were 161 in the control group, and 58 in the test group. The candidates varied from 20 to 59 years of age, and were divided into 2 age-groups—20-39 and 40-59 years. Members of the 3 racial groups (White, Cape Coloured and Bantu) living in Cape Town were studied.

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The Outpatient Group

In this group, 149 males were studied. There were 117 controls and 32 subjects with ischaemic heart disease. Apart from the subjects with heart disease, none of the men studied were outpatients in the accepted sense of the word; they were all healthy and not under the surveillance of a doctor. They will, however, for convenience, be referred to as part of the outpatient group. The patients with ischaemic heart disease all had had a myocardial infarct many months or years previously, and about half of them were being given anticoagulant therapy (phenindione). The remainder were not having such therapy, nor had they received any anticoagulant therapy within 6 months of the test being performed.

All the outpatient candidates were interviewed and a full clinical examination was performed. This included an examination of the pulse; blood-pressure readings; auscultation of the heart; and measurement of the height and weight, and the circumference of the right arm. The skinfold thickness was

assessed at 2 sites—the mid-point of the right arm posteriorly over the triceps, and posteriorly below the angle of the scapula. The caliper was standardized to record 0 - 250 kg., and the mean of readings for each site was recorded. An electrocardiogram was obtained on each candidate.

A dietary survey, with particular attention to the intake of fat, was also undertaken. At the same time, certain relevant sociological information was obtained, such as a family history of ischaemic heart disease; income; smoking habits; amount of exercise; consumption of alcohol; and, in the case of the Bantu subjects, the duration of residence in an urban area.

The Inpatient Group

Patients with any form of gastro-intestinal pathology were not considered for the test; this included peptic ulceration. No patient with cardiac, renal, hepatic or hypertensive disease was included. Patients with chest disease formed the majority of the subjects with medical illnesses, while the remainder was made up of patients recovering from herniorrhaphies, haemorrhoidectomies and a variety of minor orthopaedic procedures. All were tested on the day before being discharged from hospital. Of the 70 inpatients studied, 44 formed the control group.

All the 26 test cases had had recent (within 1 month of the test) myocardial infarction. All were on phenindione (dindevan) therapy. Heparin had not been given.

The candidates all underwent a full clinical and electrocardiographic examination. A survey similar to that undertaken on the outpatient group was not attempted, but particular attention was given to (*a*) whether or not the candidate had undergone an operation, and (*b*) whether or not the candidate was receiving antibiotic therapy.

TECHNIQUE OF THE TEST

The test meal and the method of performing the butterfat-tolerance test have been recorded previously.[1,2] 70 G. of butterfat were fed as a test breakfast and 5 samples of venous blood were tested—fasting, and 2, 4, 6 and 7½ hours after the test meal. The subjects were fasting during the period of the test, but those who wished to smoke were permitted to do so. The fasting serum-cholesterol levels of all the patients were recorded, using the technique of Abell *et al.*[3]

The degree of lipaemia (in turbidimetric units) was plotted against time on a graph and a curve obtained. The area under this curve was then calculated by the method of counting squares, the result being expressed as the total area (in sq. mm.) for each curve. This gave some indication of the quantity of fat circulating during the post-prandial period.[4,5] When analysing the tolerance curves, the mean total area of the curves was first compared. If significant differences were found between the various groups being analysed, a statistical analysis of the individual points on the fat-tolerance curve was made.

RESULTS

In a previous communication[2] it was reported that (*a*) patients with ischaemic heart disease have a greater and more prolonged lipaemia following the ingestion of a standard fat meal than do apparently normal controls, (*b*) no differences are noted between the 3 racial groups residing in Cape Town, and (*c*) the age of a candidate does not influence the lipaemic response to the test meal. Because no inter-racial differences were demonstrated, certain variables have been analysed irrespective of race (Figs. 1 and 2). The previous diet (with special reference to the fat content), income, smoking habits, family incidence of ischaemic heart disease, height, weight, skinfold thickness, and fasting serum-cholesterol levels, do not influence the duration or degree of the alimentary lipaemia following the test meal.

The Effect of Anticoagulant Therapy

The effect of phenindione therapy on post-prandial lipaemia was studied in those outpatients with ischaemic heart disease. There were 18 patients not on anticoagulant therapy, while

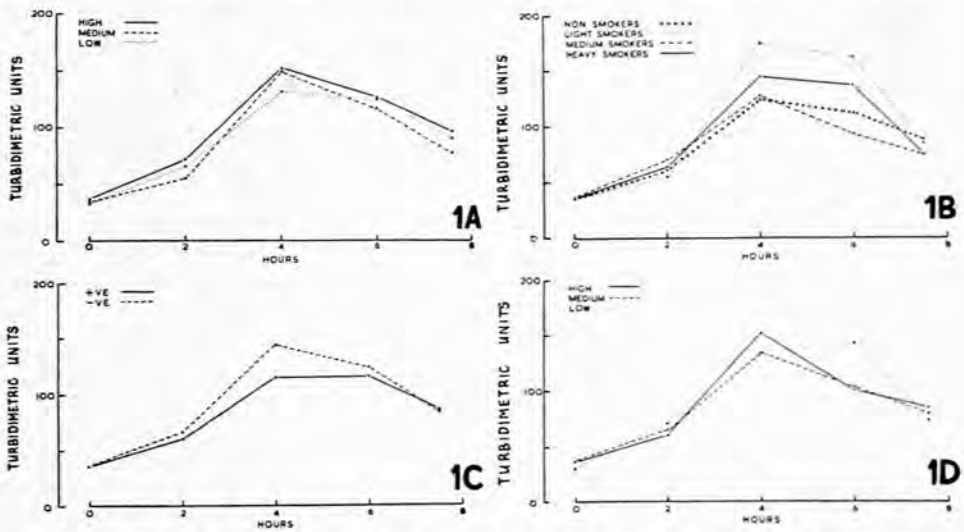

Fig. 1. Effect of certain variables on the fat-tolerance test. (A) income, (B) smoking, (C) family history of ischaemic heart disease, and (D) previous fat consumption in diet, expressed as a percentage of the total caloric intake (in outpatients). None of these influenced the fat-tolerance test.

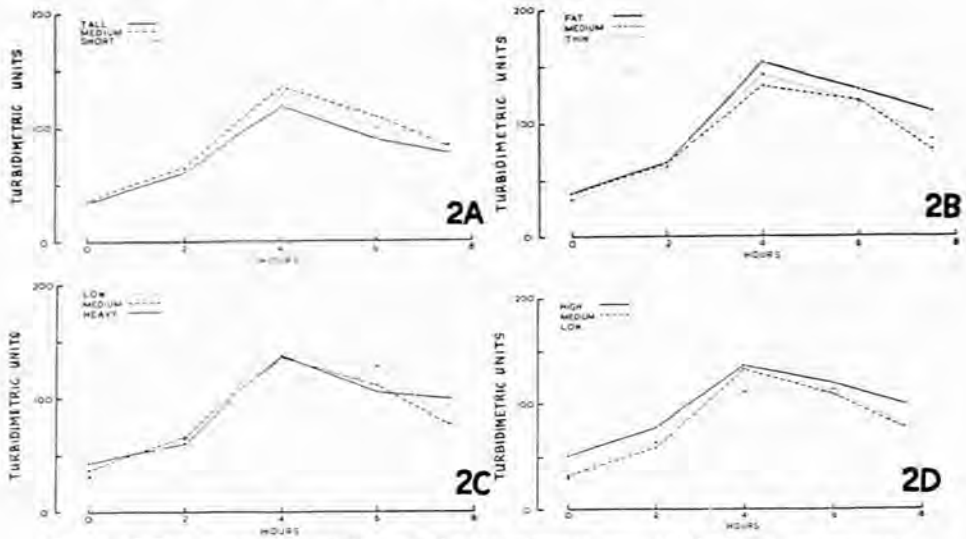

Fig. 2. Effect of certain variables on the fat-tolerance test. (A) height (in outpatients), (B) skinfold thickness, (C) weight, and (D) serum-cholesterol levels (in outpatients). None of these influenced the fat-tolerance test.

14 were receiving dindevan tablets. The analysis of the fat-tolerance curves obtained from these patients is summarized in Fig. 3. There is a significant difference between the mean total areas of the 2 groups, patients on phenindione therapy having a lessened lipaemic response. Statistical analysis of the 4-, 6-, and 7½-hour levels of the curve did not show a significant difference, although there was an indication of some difference. It would be of interest to repeat this comparison with an increased sample size.

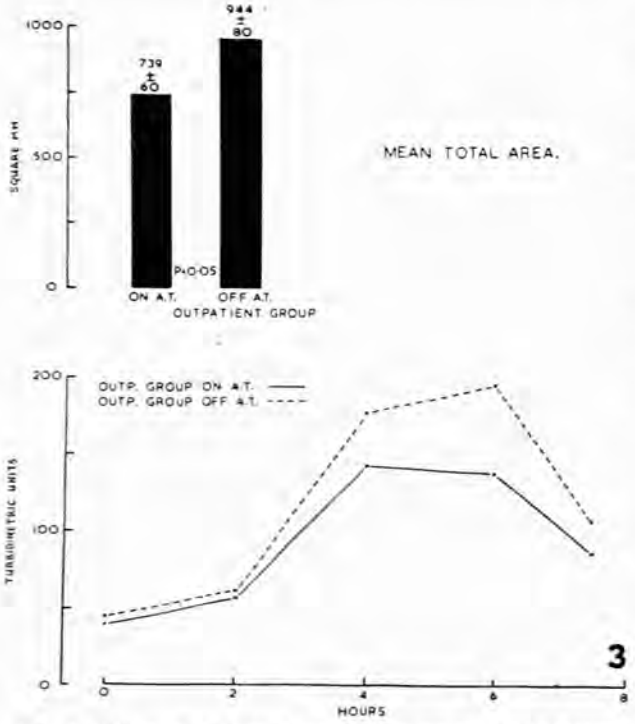

Fig. 3. Effect of anticoagulant therapy on the fat-tolerance test. Phenindione had some effect in reducing the post-prandial lipaemic response in patients with ischaemic heart disease. (A.T.=anticoagulant therapy.)

Effect of Antibiotic Therapy

Twenty-six of the inpatient control candidates were receiving antibiotic therapy at the time the fat-tolerance test was performed. With the exception of 3 subjects who were on oral broad-spectrum antibiotic therapy, the only antibiotics used were penicillin and streptomycin administered by intramuscular injection. There was no reason to believe that, at the time of the test, those subjects on antibiotic therapy were less well than those candidates not on this therapy. No antibiotics were administered during the duration of the fat-tolerance test.

The candidates on antibiotic therapy demonstrated a striking and highly significant diminution in the plasma lactescence following the test meal (Fig. 4). Further analysis of the group on antibiotic therapy showed that most of them had undergone a previous operation. There was good reason to believe that the event of an operation (of the type permitted in these tests) did not influence the fat-tolerance test (Fig. 5). In any event, even if the postoperative subjects were excluded, the difference between those on, and those not on, antibiotic therapy was still significant.

DISCUSSION

Despite wide differences in economy, food habits, dietary intake of fat and serum-cholesterol levels between the White, Cape Coloured and Bantu communities of Cape Town,[6-8] a similar lipaemic response to the test meal of fat has been found in those members of the 3 racial groups tested in this survey. It is therefore not surprising that serum-cholesterol levels, dietary intake of fat, income, and body habitus do not influence the fat-tolerance test. It follows, too, that the serum-cholesterol level and the fat-tolerance test cannot be equated. Although both are altered in the presence of ischaemic

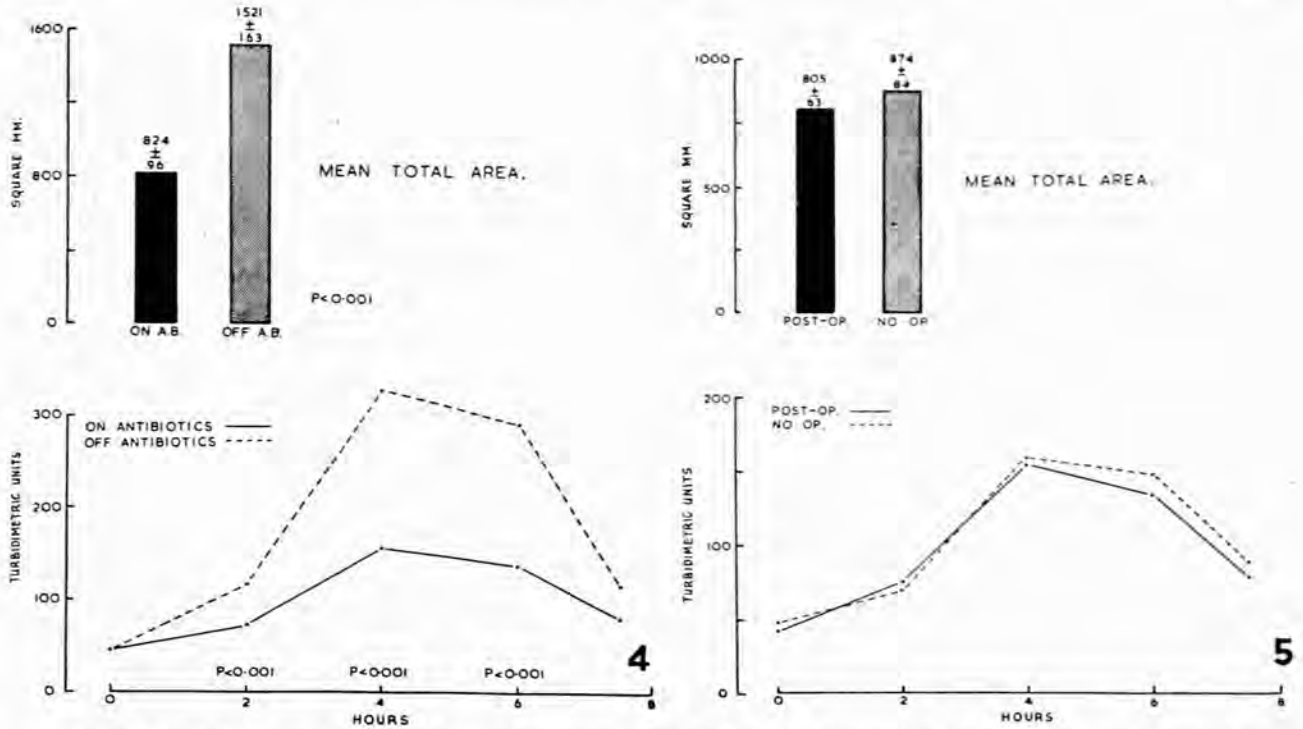

Fig. 4. Effect of antibiotic therapy (penicillin and streptomycin) on the fat-tolerance test (in inpatient controls). The antibiotics caused a significant reduction in alimentary lipaemia. (A.B. = antibiotics)

Fig. 5. Effect of an operation on the fat-tolerance test (in inpatients on antibiotics). The fact of an operation did not influence the fat-tolerance test.

heart disease, they do not appear to measure similar metabolic events.

Effect of Anticoagulants

There is no reason to believe that those candidates receiving phenindione therapy differed in any respect, other than the fact of the anticoagulant therapy, from the group not receiving this drug. Those patients not having anticoagulant therapy were not obviously taking more fat in their diet, having more or less exercise, or taking any other form of therapy. Those patients receiving anticoagulant therapy had not had a more severe myocardial infarct than the 'non-anticoagulant' group. There is at present controversy in the literature over the effectiveness of phenindione in reducing alimentary lipaemia. Horita and Loomis[9] stated positively that phenindione had no anti-lipaemic action. Osborne[10] treated a patient suffering from fat embolism with 'dindevan' and the patient recovered. He believed that the anticoagulant, in doses insufficient to lead to coagulation defects, had an antilipaemic effect. Unfortunately, little weight can be attached to the evidence from one case. In a study of the variables affecting the fat-tolerance test, Schwartz *et al.*[11] found that 3 patients on bishydroxycoumarin ('dicumarol') showed lower post-prandial turbidity levels than did 3 patients not on such therapy. At present, therefore, information regarding the effect of phenindione on alimentary lipaemia is scanty; but the results obtained from this survey indicated that the drug had some anti-lipaemic effect.

Effect of Antibiotics

No reports are available regarding the influence of antibiotics upon the fat-tolerance test. The suggestion was made by Mosonyi and others in 1951 that streptomycin had a lipaemic action.[12] The results of the present investigation certainly suggest just the reverse. Rokos *et al.*[13] reported that chlortetracycline had an inhibitory effect upon pancreatic lipase. This in turn might result in a reduced chylomicronaemia. However, all but 3 of the subjects on antibiotic therapy were receiving parenteral penicillin and streptomycin.

While antibiotics might act in many ways—by increasing intestinal motility, by affecting the intestinal cell or its enzymes, by affecting the processes occurring in the blood, or by altering the bacterial flora of the gut—it is tempting to believe that the action on the bacterial flora is responsible for their effect on alimentary lipaemia. Goldsmith *et al.*[14] reported significant lowering of the serum lipids when neomycin was administered orally. They suggested that this antibiotic produced changes in the intestinal flora, which in turn might have been responsible for the lowering of the serum lipids. An increase in the total faecal-fat excretion, free fatty acids, and soaps in patients on broad-spectrum antibiotic therapy has been reported by Faloon *et al.*[15] Decreased plasma carotene and serum cholesterol occurred during neomycin therapy.[16] From his studies on the effects of 'aureomycin' and chloramphenicol, Faloon believed that alterations in the bacterial flora of the intestine were not responsible for the steatorrhoea.[17,18] Faloon therefore be-

lieved that the effect of neomycin, at least, was to cause an 'inflammation of the jejunal mucosa'. Unfortunately, studies of the faecal flora were not undertaken. Gabuzda *et al.*[19] found no consistent quantitative or qualitative change in stool flora of patients receiving aureomycin, although these subjects manifested alterations in their nitrogen balance. However, this does not imply that similar results from stool culture will be obtained in antibiotic-induced steatorrhoea. It would seem that at present there is no certainty how antibiotics affect the absorptive functions (and particularly the absorption of fat) of the intestine.

Both penicillin and streptomycin, when administered parenterally, are able to pass freely into all the body fluids, and are found in the bile.[20] There is much evidence that parenteral antibiotics—including penicillin and streptomycin —can and do alter the flora of the gut. Fairlie and Kendall,[21] Fowler,[22] and Sanders and Kinnaird[23] have reported cases of staphylococcal enteritis following parenteral streptomycin and penicillin therapy. The value of penicillin therapy in the megaloblastic anaemias of Africans has been reported by Foy and Kondi.[24] It would appear that these antibiotics, administered parenterally, inhibit particularly the Gram-negative intestinal bacteria.[25] No faecal-fat studies or stool cultures were undertaken during the present investigation. Nevertheless, the possibility of the antibiotics having altered the bacterial flora of the gut, and thereby the absorption of fat, is one to be seriously considered. This is a field in which there is room for much work. Many questions remain unanswered, e.g. what effect would antibiotics have upon the alimentary lipaemia of patients with ischaemic heart disease; is there any difference in the bacterial flora of normal persons and those with ischaemic heart disease?

Effect of Surgery

It was hoped that, by testing the patients just before discharge, any effect of the operation itself would have passed off. The results of the investigation suggested that this aim had been achieved. There is some information pointing to a disturbance of fat metabolism in the immediate postoperative period at least. Goldenberg and Byrnes[26] fed a group of 39 patients, undergoing major extraperitoneal surgery, either radioactive triolein or oleic acid. None of the individuals tested had obvious gastro-intestinal disease. The fat was fed 24 hours pre-operatively and again 18 - 24 hours after the operation. Significant depression of the uptake of triolein in the postoperative period was found 4 and 6 hours after the dose had been administered. There were no differences in oleic-acid levels. These results suggested diminution of lipase production, rather than any depression of fat-absorbing mechanisms. The suggestion was made that the results reflected a depression in the volume of the gastro-intestinal secretions, including those from the pancreas. Another, less likely possibility, was a direct suppression of pancreatic activity. Recently, reports have appeared suggesting that a rise in fatty acids occurs in the immediate postoperative period. The secretion of a lipid-mobilizing hormone (LM) has been postulated. It is said to be released from the posterior pituitary during surgical stress, causing mobilization of the fat from the omentum.[27,28] Support for this concept came from Rudman *et al.*,[29] working with rabbits.

Because of the time interval between the operation and the performance of the fat-tolerance test, the present investigation neither confirmed nor refuted the reports quoted above.

SUMMARY

Oral butterfat-tolerance tests were performed upon 219 males—70 inpatients and 149 subjects who were working and were not patients in the hospital. Members of the 3 racial groups in Cape Town (White, Cape Coloured and Bantu) were tested. Males with no evidence of ischaemic heart disease formed the control group, while those with clinical evidence of ischaemic heart disease formed the test group. All the inpatients were between 40 and 59 years of age, while the non-hospital (outpatient) group consisted of candidates between the ages of 20 and 59 years.

Differences in income, diet, smoking habits, family incidence of ischaemic heart disease, height, weight, skinfold thickness and serum-cholesterol levels, do not influence the test.

Those patients with ischaemic heart disease who are receiving phenindione (dindevan) therapy show less postprandial lipaemia than those patients not on anticoagulant therapy.

The parenteral administration of penicillin and streptomycin results in a considerable reduction of the lipaemia following the ingestion of fat.

In the individuals tested, the event of an operation does not influence the fat-tolerance test.

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