though the technique used (the polyethylene glycol precipitation of $^{125}\text{Clq}^1$) may have been insufficiently sensitive.

These interesting possibilities are open to experiment. Whatever the explanation the phenomenon is of considerable clinical importance and emphasises the need for prevention and early diagnosis and treatment of infection in anti-GBM disease. We suspect that reports describing the development of Good-pasture's syndrome after upper respiratory tract infection are also examples of the same type of phenomenon.^{31 32} The extent to which similar events occur in other forms of allergic disease deserves study.

We should particularly like to acknowledge the help of Dr C B Wilson of the Scripps Clinic, La Jolla, for performing anti-GBM antibody assays for us. We also thank the physicians who referred patients to us and Miss Sally Gibbons and Mrs J MacAuley for expert technical help.

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(Accepted 21 July 1977)

Hepatic structure and function after modified jejunoileal bypass surgery for obesity

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British Medical Journal, 1977, **2**, 726-729

Summary

The most serious adverse effect of standard intestinal bypass for obesity is the high incidence of hepatic dysfunction and death from hepatic failure. We therefore examined the long-term effects of a modified form of jejunoileal bypass (in which a greater continuous length of ileum is retained), on liver function in 120 patients.

Substantial weight loss ($119.0 \pm \text{SD } 23.3 \text{ kg}$ to $82.3 \pm 18.8 \text{ kg}$) occurred during the first nine months after surgery, accompanied by a significant rise in serum concentrations of bilirubin, alanine transferase, and alkaline phosphatase, and a significant reduction in albumin concentrations. Biochemical changes were unrelated to weight loss or halothane anaesthesia. After weight stabilisation liver function reverted to normal, and four years after

bypass sulphobromophthalein retention and hepatic histology did not differ from those in obese controls. There were two postoperative deaths. Three other patients died during the period of rapid weight loss with severe hepatic steatosis.

While transient mild impairment of liver function is common after modified jejunoileal bypass, clinically significant hepatic dysfunction is a rare and unexplained early complication.

Introduction

Obesity, the major nutritional disorder in affluent western societies, is an increasingly important health hazard. Unfortunately, its correction has proved to be a formidable problem as medical measures provide only temporary relief. Thus surgical management is an appropriate consideration for selected patients with gross obesity who have failed to lose weight under strict medical supervision.

Various intestinal bypass procedures have been used to achieve weight reduction. The first operation introduced, jejunocolic bypass, has now been abandoned because of its unacceptably high morbidity and mortality, and replaced by jejunoileal bypass. The standard operation of Payne and De Wind,¹ in which 35 cm (14 inches) of proximal jejunum is anastomosed to 10 cm (4 inches) of terminal ileum, has undoubtedly proved effective, and produces substantial weight loss accompanied by gratifying psychosocial improvement.²

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Nevertheless, various complications of bypass surgery have been recognised, the most important of these being the high incidence of hepatic dysfunction and death from hepatic failure.³⁻⁶

We have introduced a more radical operation than the standard procedure, but which still retains a greater continuous length of ileum.⁷ We report our experience of this modified procedure over five years, with particular reference to its effects on liver structure and function.

Patients and methods

Obese patients were selected for bypass if they had continually failed to respond to conventional weight reduction treatment, were emotionally stable, and aware of the implications and potential complications of bypass surgery. There was no arbitrary weight requirement, but on average our patients were twice their matched population mean weight. Before selection for bypass each patient underwent psychiatric evaluation to determine his or her emotional suitability and attitudes to operation. Complications of obesity, such as hypertension or maturity-onset diabetes were not a contraindication, but no patient with liver disease or a history of alcohol abuse was accepted for surgery.

Since the programme began in 1971 120 obese patients aged between 22 and 60 years have undergone bypass surgery at St George's Hospital. We monitored serial data on weight and biochemical changes for the first 35 patients for up to five years after modified bypass procedure. The group included 33 women (mean age 37 years, range 22-60) and two men (aged 41 and 51 years).

The operation was a modification of the standard "14/4" end-to-side jejunio-ileal bypass.¹ In the standard procedure the jejunum is divided at 14 inches (35 cm) from the duodenojejunal junction, and anastomosed end to side to the ileum 4 inches (10 cm) from the ileocaecal sphincter. In our patients only 14 inches (35 cm) of small bowel was left in circuit, either by performing a "4/10" (anastomosing the proximal 4 inches (10 cm) of jejunum end to side to the terminal 10 inches (25 cm) of ileum), or a "7/7" procedure (anastomosing the proximal 7 inches (17.5 cm) of jejunum end to side to the terminal 7 inches (17.5 cm) of ileum). Although more radical than the standard Payne and De Wind operation, leaving only 35 cm of approximately 350 cm of the small bowel in continuity, a greater length of ileum is retained to preserve vital non-caloric absorptive functions.

Results

Weight—Substantial weight reduction occurred during the first nine months after bypass surgery (fig 1), the average weight loss being 37 kg from a mean preoperative weight of 119 kg. One year after bypass a new steady state was achieved. This new weight appeared to be maintained for up to 5 years, the present length of follow-up.

Liver function—Serial biochemical data obtained from the first 35 obese patients who underwent the modified bypass operation (thirty "4/10", five "7/7") is shown in fig 2. None of these patients developed jaundice or liver failure. Nevertheless, small but significant increases in plasma concentrations of bilirubin ($9.1 \pm \text{SD } 4.3 \mu\text{mol/l}$ to $13.8 \pm 7.0 \mu\text{mol/l}$ ($0.53 \pm 0.25 \text{ mg/100 ml}$ to $0.81 \pm 0.41 \text{ mg/100 ml}$); ($P < 0.01$);

FIG 1—Changes in weight (mean $\pm$ standard error of mean) in 35 patients up to 60 months after modified jejunioileal bypass operation.

FIG 2—Mean ($\pm$ standard error of mean) plasma concentrations of bilirubin, alkaline phosphatase, alanine transferase, and albumin in 35 patients up to 60 months after modified jejunioileal bypass. Asterisks denote significant change from control (preoperative) values.

Conversion: SI to traditional units—Serum bilirubin: $1 \mu\text{mol/l} \approx 0.06 \text{ mg/100 ml}$; albumin: $1 \text{ g/l} = 0.1 \text{ g/100 ml}$.

alkaline phosphatase ($8.4 \pm 2.9 \text{ KAU/100 ml}$ to $13.0 \pm 5.5 \text{ KAU/100 ml}$); ($P < 0.001$); and alanine transferase ($15.7 \pm 11.9 \text{ IU/l}$ to $36.9 \pm 32.3 \text{ IU/l}$); ($P < 0.01$) were detected in the nine months immediately after bypass. A significant reduction in plasma albumin was noted at six months ($35.1 \pm 3.8 \text{ g/l}$ to $31.6 \pm 8.7 \text{ g/l}$ ($3.5 \pm 0.4 \text{ g/100 ml}$ to $3.2 \pm 1.0 \text{ g/100 ml}$); ($P < 0.05$), and a similar reduction observed 12 months postoperatively. Thereafter biochemical values returned to the normal preoperative ranges. Biochemical changes were unrelated to post-operative weight loss. Two-thirds of the patients received halothane anaesthesia at the time of bypass surgery, but there was no significant difference between the halothane and non-halothane groups in subsequent liver function. In an unselected group of 12 patients studied between four and five years after intestinal bypass, sulphobromophthalein (5 mg/kg) retention did not differ from that in a similar group of 12 obese patients examined before operation.

Hepatic histology—Variable amounts of fat were present in needle biopsy specimens from the livers of obese patients before and after bypass. There was no other consistent histological abnormality, and in the group of patients studied after bypass there was no evidence of increased hepatic fibrosis or cirrhosis. In a "blind" evaluation of needle biopsy specimens from the livers of 28 obese patients before bypass surgery, and from 13 patients matched for age and sex examined four to five years after modified jejunioileal bypass, visual assessment of the degree of fatty change showed this to range widely from zero to about 75%. Over three-quarters had some degree of fatty metamorphosis, but there was no difference in the extent or distribution of hepatic fat between the two groups. Electron microscopy of the post-bypass biopsy specimens showed no significant abnormalities of the hepatocyte cytoplasmic organelles except for the presence of large fat droplets.

Deaths—There were five deaths in the series of 120 patients. Two of these followed massive postoperative pulmonary embolism. The three late deaths all occurred within nine months of bypass surgery and were associated with repeated vomiting, rapid weight loss, and extensive fatty change found in the liver at necropsy. In two of these the fatal outcome was preceded by persisting abnormalities in liver function and ultimately frank jaundice. Case histories of these three patients are presented below.

Case 1—A woman aged 56, weight 136 kg. Preoperative liver biopsy

showed extensive (75%) fatty infiltration, and after a "7/7" bypass operation she had rapid and excessive weight loss (32 kg in three months). Recurrent vomiting necessitated several admissions to hospital. She became progressively weaker, and frankly jaundiced with a maximum bilirubin concentration of 248 $\mu\text{mol/l}$ (14.5 mg/100 ml) five months after bypass, about 10 days before her death. HBsAg was not detected in serum. Serial changes in other liver function values and weight are shown in fig 3. The patient developed pulmonary oedema and died while being fed intravenously. At necropsy the liver was grossly enlarged and fatty. Microscopical sections showed almost complete replacement with fat, cholestasis (both intracellular and bile thrombi), and moderate acute inflammatory changes in the portal triads.

FIG 3—Changes in weight and in plasma concentrations of albumin, alanine transferase, and alkaline phosphatase in the two patients who developed jaundice and died after modified jejuno-ileal bypass. Dashed line indicates values for patient 1, black line indicates values for patient 2; shaded area indicates control range (mean $\pm$ standard error of mean) derived from values for first 35 patients.

Case 2—A man aged 23, weight 155 kg. No preoperative liver biopsy was performed. After a "7/7" bypass operation he lost 72 kg in eight months, vomited frequently (although this was initially concealed from his doctors), and became progressively weaker. Abnormal results of liver function tests were noted one month after bypass (fig 3). Mild jaundice was first observed at five months, and bilirubin concentrations gradually rose to 145.4 $\mu\text{mol/l}$ (8.5 mg/100 ml) at the time of death nine months after bypass. Test results for HBsAg were negative. Death occurred after cardiac arrest during intravenous feeding. Postmortem examination showed almost complete fatty degeneration of the liver. There was also appreciable cholestasis, focal liver-cell necrosis, and occasional foci of polymorphs.

Case 3—A woman aged 32, weight 194 kg. Extensive fatty change (75%) was noted in the liver biopsy specimen obtained before a "4/10" bypass operation, which was followed by rapid weight loss (49 kg in the first three months), repeated vomiting, and diarrhoea. This persisted after moving to another area, and, although debilitated, she refused to attend for regular supervision, and died nine months after operation during an influenza-like illness. Results of liver function tests were not available, but at necropsy the liver appeared grossly fatty.

Discussion

Most patients fared well after modified jejunoileal bypass, and were satisfied with the outcome. The substantial initial weight loss achieved was comparable with that reported after the standard operation, and gratifyingly seems to have been maintained for up to five years (the period of follow-up), being accompanied by considerable psychosocial improvement. Nevertheless, jejunal bypass is a major undertaking, for which careful patient selection and postoperative follow-up is essential; and the undoubted benefits for the majority were obtained at the expense of a certain morbidity and mortality.

Initial experience of jejunoileal bypass suggested that this procedure, in contrast to jejunocolic bypass, was not complicated by significant hepatic dysfunction.⁸ Subsequent reports have

shown that this is not the case. There has been no agreement on the incidence of hepatic dysfunction, however, and little information about the long-term effects of jejunoileal bypass on liver function and structure. In various reports from the USA two of 24 patients died of hepatic failure,³ and six of 36 patients developed overt jaundice, of whom one died in hepatic coma and two others developed portal hypertension and ascites.⁴ Five non-alcoholic obese patients developed progressive hepatic dysfunction and cirrhosis, of whom four died in hepatic failure despite undoing the bypass.⁵ In the largest series reported from the UK there were 12 deaths in 182 patients.⁶ Of the six deaths attributable to complications of jejunoileal bypass, five were associated with liver failure, severe fatty degeneration, or cirrhosis. A further three patients developed cirrhosis.

Compared with these reports, hepatic dysfunction after our modified operation was relatively infrequent, and interestingly none of our patients subsequently developed cirrhosis. Whether these differences arose from patient selection or from the theoretical advantages of the modified operation has yet to be determined. Nevertheless, the present report, based on a substantial series of patients followed over five years, clearly shows that adverse changes in liver function occur during the period of weight loss immediately after surgery. These biochemical changes occur at a time when 95% of post-bypass patients develop moderate to severe fatty metamorphosis of the liver,⁹ and the concentration of hepatic triglycerides doubles during this period.¹⁰ Moreover, those of our patients who became frankly jaundiced and developed extreme hepatic steatosis did so at this time. Thus, the occasional occurrence of frank jaundice and liver failure may be regarded, not as an idiosyncratic response to bypass, but indicative of latent hepatic dysfunction.

Nevertheless, post-bypass hepatic impairment seems to be temporary. Liver function in the vast majority of patients reverted to the preoperative state when a new steady weight was achieved, and remained so throughout the remainder of the follow-up. Although histological abnormalities (primarily fatty change) were present in liver biopsy specimens obtained four to five years after operation, the appearances were not noticeably different from those obtained preoperatively. Our histological findings agree with those of Salmon and Reedyk,⁹ who observed that the incidence of fatty infiltration decreased after one year, so that 1500 to 2000 days after operation the incidence of hepatic steatosis had returned to that seen preoperatively. Thus, earlier conflicting reports on the effects of jejunoileal bypass on liver structure and function may have been due to failure to distinguish between the immediate and longer term effects of bypass.

Further careful evaluation of the effects of intestinal bypass is required before patients at greater risk of developing significant hepatic dysfunction may be accurately identified. Our experience emphasises the need for careful patient supervision, particularly during the early period of weight loss after bypass. Frequent or persistent vomiting accompanied by rapid and excessive weight loss are warning signs which should not be ignored. Among our series of patients, few had an unsatisfactory outcome. All three who died were heavier than the average patient undergoing bypass, however, and in the two who had a preoperative liver biopsy fatty changes were more extensive than usual.⁹ Although persistently abnormal liver function was noted in both patients who ultimately became jaundiced and died with gross hepatic steatosis, biochemical abnormalities showed no consistent pattern, and were initially unremarkable.

Our findings failed to implicate halothane anaesthesia, the extent of postoperative weight loss, or hepatitis B infection in the pathogenesis of hepatic dysfunction after bypass, and the phenomenon remains unexplained. There is an urgent need for a better understanding of the factors responsible. Such information might allow the treatment of hepatic dysfunction by appropriate medical measures, or its prevention by refinements in surgical technique.

We thank the patients who took part for their co-operation, and

Dr T R Terry, Dr Sheila Goldsworthy, and Miss Mary Bulbeck for their help.

The study was partly supported by the St George's Hospital Medical Research Fund.

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(Accepted 26 July 1977)

Oral contraceptive use and venous thromboembolism : absence of an effect of smoking

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British Medical Journal, 1977, **2**, 729-730

Summary

We conducted a case-control study to test the hypothesis that women smokers who use oral contraceptives have an increased risk of developing venous thrombosis. Patients and controls were drawn from two sets of hospital patients already included in the Boston Collaborative Drug Surveillance Programme. Sixty patients with uncomplicated thromboembolism were matched with 180 controls with other diagnoses; all were premenopausal women taking oral contraceptives. Patients with conditions that might predispose to thromboembolism or be related to smoking were excluded. We found no association between smoking habits and thromboembolism. Similarly, we found no association between thromboembolism, smoking, and duration of oral contraceptive use.

Thus we conclude that differences in fibrinolytic activity between smokers and non-smokers are not major factors in the aetiology of uncomplicated thromboembolism in women using oral contraceptives.

Introduction

Several studies have shown a substantial positive association between thromboembolic disease and the use of oral contraceptives.¹⁻⁴ This association may be explained by the enhanced concentrations of coagulation factors shown in the blood of women taking oral contraceptives.⁵ A recent report suggests that this increase in concentrations of coagulation factors in oral contraceptive users is associated with a compensatory increase in fibrinolytic activity in non-smokers, but not in smokers.⁶ This raises the possibility that smoking may predispose to thromboembolism in oral contraceptive users. We undertook a study to test this hypothesis, and report the results.

Patients and methods

We obtained information from two independent sets of patients studied by the Boston Collaborative Drug Surveillance Programme. The first set (source 1) consisted of patients admitted consecutively to selected acute medical wards in hospitals in the USA. The second set (source 2) consisted of patients admitted consecutively to general medical and surgical wards of 24 hospitals in the greater Boston area in 1972. Patients were excluded from the second set if they had been admitted to hospital in the preceding three months, were too ill to interview, or were admitted for less than 72 hours, and so may have missed interview.

Patients were interviewed by trained nurses, who obtained information on demographic characteristics, personal habits (including smoking and alcohol consumption), and history of medication. Diagnoses at discharge were later obtained from the hospital records. Details of the exact methodology applied in the two studies have been given elsewhere.^{1,7}

We confined our analyses to patients who were premenopausal oral contraceptive users. We further excluded patients with diabetes mellitus, obesity, acute myocardial infarction, lipid abnormalities, varicose veins, or pulmonary disease other than thromboembolic—all conditions which might predispose to the development of thromboembolism or be related to cigarette smoking. Also excluded were patients whose thromboembolism was secondary to trauma or surgical procedures. There remained for study a total of 63 patients admitted primarily because of uncomplicated deep venous thrombosis or pulmonary thromboembolism or both. For each such patient, three control patients were sought from the set of premenopausal oral contraceptive users. Patients and controls were matched for age (within a five-year tolerance), study source, and according to where they had been admitted to hospital. Sixty patients were successfully matched, although 14 of the resulting 180 controls were not matched for where they had been admitted to hospital simultaneously with the other factors. A detailed review of these 14 controls showed that their inclusion in the study did not affect the final results.

Among the 180 controls the primary diagnosis at discharge was gastrointestinal disease in 54 (30%), injury or orthopaedic conditions in 23 (13%), infection in 18 (10%), neurological disease in 14 (8%), genitourinary disease in 13 (7%), cardiovascular disease in 11 (6%), and haematological disorders in 9 (5%). Various other conditions were

TABLE 1—Relation between smoking habits and thromboembolism in oral contraceptive users

	Patients with thromboembolism (n = 60)	Controls (n = 180)
Non-smokers*	26 (43%)	72 (40%)
<20 cigarettes day	29 (48%)	86 (48%)
≥20 cigarettes day	5 (8%)	22 (12%)

*Includes former smokers who had currently abstained for over one year.

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