adding yet another case to five reported from this unit in 1970.¹—I am, etc.,

BRYAN N. BROOKE

Professorial Surgical Unit,
St. George's Hospital,
London S.W.17

¹ Javett, S. L., and Brooke, B. N., *Lancet*, 1970, 2, 126.

Place of Vasectomy

SIR,—The letter "Doctors and Overpopulation" (8 January, p. 108), in which a call is made for a massive increase in the provision of vasectomy, again urgently brings to the fore the consideration of the place of vasectomy as potentially the principal method of family limitation and the prevention of "overpopulation pollution."

The recent correspondence in your columns about vasectomy techniques was entirely from consultant surgeons who are also responsible for the many patients on very long lists awaiting skilled surgical procedures. It therefore seems appropriate at this time to relegate vasectomy to a more appropriate level and to regard it simply as a family planning procedure on a par with the insertion of an intrauterine contraceptive device, but without the attendant risks of uterine perforation, pelvic infection, or the need for regular replacement of the intrauterine contraceptive device.

Vasectomy cannot be equated for ease and safety with tubal ligation, which requires a general anaesthetic and the valuable time of a gynaecologist, and which in 43% of cases (8 January, p. 84) incurs further gynaecological treatment. Vasectomy can be safely, quickly, and painlessly performed by a trained general practitioner or family planning clinic doctor and usually requires no subsequent medical supervision, the semen tests being laboratory procedure. It is especially uncomplicated using the following technique:

A tablet of diazepam 5 mg is required as a premedication for anxious patients and the 1% lignocaine with adrenaline is given through a $\frac{1}{8}$ in (16 mm) 25 S.W.G. needle on a 2 ml syringe. This enables the sheath of the vas to be anaesthetized while the site of the single midline scrotal incision is held over each vas in turn by the fingers of the left hand; 2 ml of lignocaine is usually found to be adequate for the entire operation, some of it sometimes being given into the sheath when it is exposed. After exposing the vas with atraumatic vasectomy forceps a small section is removed and the cut ends crushed, doubly ligated, and allowed to slip back into the sheath. A single, inverted, fine catgut mattress suture with the knot buried closes the skin and a dressing is not required after the first day.

With waiting lists for this operation running into several thousands I suggest the formation of an association for the promotion of vasectomy, and I would be pleased to hear from other doctors similarly interested.—I am, etc.,

MICHAEL ALTMAN

1012 High Road,
London N.20

Trial of Clofibrate

SIR,—Dr. H. A. Dewar and Dr. M. F. Oliver and their colleagues are to be warmly congratulated on their clinical trials on clofibrate (25 December 1971, pp. 767 and 775). We are indebted to them for their detailed work and careful conclusions.

Before accepting clofibrate as a major treatment for patients with angina or for those who have had a myocardial infarction there are certain problems which need stating. There is a danger that some patients and doctors will consider that the new pill will make other measures unnecessary. Coronary disease is largely an environmental disease and there is good evidence that cigarette smoking and lack of exercise are the most important factors. In the Scottish series the control patients who were non-smokers had fewer events than the patients treated with clofibrate who were smokers. The Newcastle group noted that not a single lifelong non-smoker died suddenly. There is also evidence accumulating that controlled exercise may improve the outlook for patients after a myocardial infarction or with angina.

If we decide that the evidence warrants the use of clofibrate in certain categories of our patients do not let us forget advice on the patient's way of living, particularly on his smoking habits and his exercise.—We are, etc.,

K. P. BALL
M. W. McNICOL

Central Middlesex Hospital,
London N.W.10

SIR,—As Dr. M. F. Oliver and his colleagues point out in their commentary (25 December, p. 775) on the two trials using clofibrate in the secondary prevention of cardiac infarction, this drug lowers not only the levels of blood cholesterol and triglyceride but also, perhaps more importantly, of free fatty acids. We would like to suggest some ways in which a sustained reduction of free fatty acids might account for some of the otherwise puzzling distribution of benefits from clofibrate.

Aside from their possible long-term atherogenic properties,¹ there are several ways in which elevated free fatty acid levels can directly affect the heart. Firstly, they can make the myocardium more sensitive to the action of catecholamines,² and precipitate a "sudden" arrhythmic death. The outstanding reduction of sudden deaths in both trials, particularly among smokers, is interesting in this context, as smoking abruptly raises free fatty acid levels by causing noradrenaline secretion.³

Secondly, free fatty acids suppress the myocardial uptake of glucose in man.⁴ The increased utilization of fat raises the oxygen requirements of the heart muscle which might initiate angina and oedema of the anoxic tissue, resulting in retrograde thrombosis.⁵ This is especially likely to occur where the coronary circulation is barely adequate, as in the "all-angina" groups who benefited so markedly from the drug. Also the progression of crescendo angina may possibly be explained on the basis of each attack providing a further emotional stimulus for catecholamine release, raising free fatty acid levels, leading in turn to more myocardial anoxia, more anginal pain, further increased free fatty acid levels, and so perpetuating the vicious circle until infarction occurs. A reduction in the frequency or severity of angina induced by emotion rather than by effort in patients taking clofibrate would support this view. Many emotional situations raise free fatty acid levels,⁶ while non-violent exercise can reduce them.

Other questions arise from these con-

siderations—whether the benefit was greater in overweight patients, who tend to have higher free fatty acid levels; whether the free fatty acid reduction on this drug is maintained; and whether there was any difference in the postmortem findings, in view of the inevitable difficulty of classifying the cause of death into "sudden" and "infarction" groups without morbid anatomical data in many of the patients who died. While appreciating practical difficulties incumbent in a large study of this nature, much information on the presence or absence of thrombus or appearances compatible with retrograde spread of infarction might clarify some of the results obtained.

In view of these unresolved questions it might be advisable to avoid concluding too definitely that the protection afforded by clofibrate is unrelated to the effect of clofibrate on serum lipids before the relevance of the most underestimated of the lipid fractions, free fatty acids, has been more fully investigated.—We are, etc.,

MALCOLM CARRUTHERS

Department of Chemical Pathology,
Institute of Ophthalmology,
London W.C.1

PETER TAGGART

Institute of Clinical Research,
Middlesex Hospital,
London W.1

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Truncal Vagotomy and Pyloroplasty

SIR,—The report from Leeds and York on the results of truncal vagotomy and pyloroplasty (1 January, p. 7) suggests that in Britain gastrectomy for duodenal ulcer is a more satisfactory operation, according to Visick grading, than vagotomy and drainage procedures, particularly when the drainage is by pyloroplasty.

This excellent review will be read by many surgeons who are, or will be, working overseas, and I am concerned lest it may encourage those working in developing countries to revert to the old policy of gastrectomy for duodenal ulcer which was prevalent in the larger centres in those countries 20 years ago. While it proved an excellent operation from the point of view of preventing recurrent ulceration it often proved a most crippling operation in people whose normal staple diet was bulky (rice, maize, tapioca) by virtue of the resulting reduced capacity for food. This reduction in capacity is less troublesome in patients who take the Western type of refined concentrated carbohydrate diet, because a reduction in food capacity need not result in a serious fall in caloric intake but can be very troublesome in patients who depend for their calories on being able to take an adequate quantity of bulky food, particularly when they often rely on one large meal a day. There was no doubt that in south India patients managed better with a vagotomy and drainage procedure.¹ A follow-up in Mysore showed that 34% of gastrectomy patients had normal capacity for food com-

pared with 61% of vagotomy and drainage patients. In the gastrectomy group only 30% gained weight compared with 54% of the other group.

In the vagotomy and drainage group the results were similar after either truncal or selective vagotomy and after either pyloroplasty or gastrojejunostomy. True dumping as distinct from small-stomach syndrome is rare in patients on a rice diet, and was seen less often in the vagotomy and pyloroplasty patients than after vagotomy and gastrojejunostomy or gastrectomy.—I am, etc.,

FRANK I. TOVEY

Basingstoke and District Hospital,
Basingstoke,
Hants

¹ Tovey, F. I., *British Journal of Surgery*, 1969, 56, 281.

Fatal Hepatic Necrosis and Halothane

SIR,—As it is still debated¹ whether halothane is hepatotoxic or not, we would like briefly to report two cases.

A woman, 55 years old, had been operated on five years before for varicose veins under thiopentone-halothane-N₂O-O₂ anaesthesia with pethidine and atropine as premedication. On the present occasion biopsy was performed for a breast tumour under the same anaesthetic. As cancer was found, radical mastectomy was performed nine days later under thiopentone-suxamethonium-pethidine-halothane-N₂O-O₂ anaesthesia with pethidine and atropine as premedication. Fever was not noticed between the operations, but her temperature was taken on the day before the second operation only, and was then 37.4°C. She had fever, 38.9°C, on the first three days after the second operation and jaundice was noticed on the fourth, when the temperature had begun to fall. She developed liver insufficiency and died 28 days after the second operation. Necropsy revealed massive centrilobular liver necrosis (liver weight 950 g), acute pancreatic necrosis, cholaemic nephrosis, and haemorrhagic diathesis. No metastases were found.

The second patient, a woman 54 years old, was operated on for varicose veins of both legs with stripping and ligature in two stages with four days' interval between them, both operations being performed under thiopentone-halothane-N₂O-O₂ anaesthesia with pethidine and atropine as premedication. Between the operations she was febrile (maximum 37.7°C). On the fifth day after the second operation her temperature was 40.7°C, and jaundice was noticed on the ninth day. She developed liver insufficiency and died on the 17th day after the second operation. Necropsy showed massive centrilobular liver necrosis with congestion (liver weight 1,570 g), acute pancreatic necrosis, cholaemic nephrosis, pulmonary oedema, and haemorrhagic diathesis with multiple erosions of the stomach.

No contacts with jaundiced persons were known. The first patient was given 450 ml blood during her mastectomy. Of pertinent drugs, the first patient had been taking meprobamate, paracetamol, and cyclopenthiiazide fairly recently. The second patient had had hydrochlorothiazide and a multivitamin preparation with caffeine.

Cholestatic jaundice has been reported following meprobamate treatment.^{2,3} Overdosage of paracetamol has occasionally resulted in fatal liver necrosis,⁴ and this can also be produced in rats with large doses.⁵

Liver damage following cyclopenthiiazide does not seem to be described. The related substance chlorothiazide is well known to be able to precipitate liver coma in patients with cirrhosis. It has been reported occasionally to produce severe hepatic injury, with necrosis⁶ and cholestatic jaundice.^{6,7}

Neither of the patients had eosinophilia. The only morphological material available was from the necropsies. Electron microscopy of the livers showed extensive autolysis, and there were no possibilities to distinguish possible pathognomonic changes in the mitochondria.⁸ Examination for Au-antigen was not possible at that time (1966), and no serum is preserved.

The Swedish Adverse Drug Committee considered the relationship between the repeated halothane anaesthetics and the fatal hepatic necroses to be established (*säkerställd*) in these two cases.⁹ We are inclined to agree. The finding of acute pancreatic necrosis in cases of fatal hepatic necrosis ascribed to halothane has been reported previously.¹⁰—I am, etc.,

UNNE STENRAM

Department of Pathology,
University of Uppsala,
Sweden

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Banana and L-Dopa

SIR,—Upper alimentary side effects of L-dopa therapy are common. Dr. D. Riddoch (1 January, p. 53) described a patient with gastritis, probably due to this drug. Others have noticed anorexia,¹ nausea, vomiting, complications in coexistent peptic ulcers,² and an increased consumption of sweets with a subsequent rise in the dental caries rate.³ The vomiting of liquorice-coloured material has also been reported,⁴ and one such patient was recently encountered who produced this symptom whenever he swallowed a banana in addition to his levodopa tablet.

This phenomenon prompted the following experiments. Powdered levodopa was mixed with banana, banana plus tap water, banana plus saliva, and banana plus vomitus at room temperature. In all cases the following colour changes resulted—a faint pink, followed by a bright brown, then a dark brown, then a grey, and, finally, a liquorice-like black. The colour changes started very rapidly but the speed of the complete series of changes seemed to depend on the surface used for the experiment—being over within minutes on a scalpel blade, slower on a wooden spatula, but taking several hours in a plastic container. Such colour changes did not occur in the absence of levodopa.

Serotonin is present in banana and human brain tissue⁵ but no significant colour changes resulted when levodopa was mixed with serotonin creatinine sulphate. The

above colour changes also occurred when powdered L-dopa was mixed with pieces of grape and plum. It seems possible that certain enzyme systems present in some fruits cause chemical degradation changes in levodopa, and it may be that the metal in the scalpel blade catalyzed such a reaction.—I am, etc.,

HENRY A. GARFINKEL

St. Mary's Hospital,
London W.C.2

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Fibrin Degradation Products in Hypoxic Full-term Neonates

SIR,—In their article entitled "Coagulation Defects in Hypoxic Full-term Newborn Infants" Dr. M. A. Chadd and other (27 November 1971, p. 516) reported, among other things, a significant correlation between a low Apgar score (≤ 5) and raised levels of fibrin degradation products (F.D.P.). During the last few years we have been especially interested in fibrinolysis in newborns.¹ We have assayed F.D.P. with Niléhn's immunochemical method² in serum from blood collected in tubes containing aminocaproic acid. This method demonstrates F.D.P. down to a concentration of 5 µg/ml, and comprehensive investigations in adults at this laboratory² have shown that F.D.P. are never demonstrable in health and that, when present, they always denote disease. In our studies only levels of >10 µg/ml were accepted as being of pathological significance ("F.D.P.-positive").

We have examined 154 infants with gestational ages of 25 to 42 weeks. They were studied for F.D.P. during the first 48 hours of life. Sixty-four of the infants who had Apgar scores³ of 7-10 at 10 minutes and remained healthy afterwards were assigned to one group (H-group) while the remaining 90 with Apgar scores of less than 7 at 10 minutes and with later firm symptoms of idiopathic respiratory distress syndrome or other, mainly respiratory, symptoms were assigned to another group (S-group).

Forty of the infants were F.D.P.-positive, (11-300 µg/ml)—36 in the S-group, but only four in the H-group. The higher incidence of F.D.P.-positive cases in the S-group was studied from various angles. The occurrence of F.D.P. in the infants did not appear to vary with the presence or absence of complications of pregnancy or delivery. F.D.P. were more common in the infants with idiopathic respiratory distress syndrome than in those with other respiratory symptoms. The Table relates F.D.P. to the Apgar scores at 1 and 10 minutes using generally accepted limits³ for the various score groups. F.D.P. were significantly more common in infants with a score of 0-3 at 1 minute than in those with a higher score at that time. At 10 minutes the frequency of F.D.P.-positive cases decreased with increasing Apgar score. Determination of the arterial pH and of the blood gases (umbilical catheter) did not reveal any significant correlation between hypoxia/acidosis and F.D.P.