generally acceptable as the result of individual experience and several publications, but surely the case is overstated by Professor Scott when he says that, in a patient without prolapse, vaginal hysterectomy takes no longer than a laparoscopy, that the patients are more mobile the following day and that complications are fewer.

Laparoscopy takes 10 to 15 minutes and the patient can go home the next day. I have watched and assisted many expert vaginal hysterectomists and I often do the operation myself, but it has always taken longer than this because of the need for care with the bladder, ureters and vascular pedicles. In no case has the patient felt like going home the next day.

It is clear that Professor Scott is a most skilful surgeon but I think herein lies the great danger of his publication, for very many are not quite so skilful and if they embark on a policy of wholesale vaginal hysterectomy in young women, as he suggests, in preference to the minor operations for tubal occlusion, I am certain they will come to regret it. Many patients asking for sterilization are relatively young and both they and their husbands believe it is a minor procedure without risk.

I agree that the uterus should be removed if there is any evidence that it is abnormal and I also agree that it is usually best removed vaginally, but I am not happy about this prophylactic hysterectomy idea.

Victor Bonney wrote "The load of responsibility that a surgeon shoulders every time he performs an operation is surely great enough without adding to it by meddlesome chippings and choppings."—I am, etc.,

J. M. GATE

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¹ Bonney, V., *Textbook of Gynaecological Surgery*, 6th edn., Cassell, London, 1952.

Skin Reactions to Ampicillin

SIR,—Your leading article (22 January, p. 195) and the ensuing correspondence (19 February, p. 505) has again drawn attention to the interesting relationship between ampicillin rashes and abnormal mononuclear cells.

I have recently seen such a patient in whom the diagnosis was stage IV reticulosarcoma. This 62-year-old man developed a widespread red macular rash 10 days after ampicillin given for a urinary infection. On examination he was noted to have a generalized lymphadenopathy, later shown by biopsy to be reticulosarcoma. There were a large number of abnormal monocytoïd cells in his bone marrow compatible with this diagnosis, and his Paul-Bunnell test was negative. At the time of diagnosis he was slightly anaemic (Hb 12.6 g/100 ml) and leucopenic (W.B.C. 2,800/mm³ of which 1,550/mm³ were neutrophils and 1,000/mm³ lymphocytes). His serum proteins were normal, but unfortunately his immunoglobulin levels were not determined.

A curious feature in his case was a recrudescence of the rash, lasting only a day or so, immediately following biopsy in the area of what was thought to be a painful supraclavicular node. The biopsy was unsuccessful as the material removed proved to be a (? traumatic) neuroma. Subsequent biopsy of an inguinal node revealed the true diagnosis.

It seems that ampicillin sensitivity may be added to alcohol-induced pain as an unexplained curiosity of lymphomatous conditions, and may not be confined to infectious mononucleosis and lymphatic leukaemia. It would be interesting to know whether it occurs in Burkitt's lymphoma.—I am, etc.,

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Clofazimine in Leprosy

SIR,—In commenting on a recent trial of clofazimine in lepromatous leprosy by Dr. A. B. A. Karat and co-workers (27 November 1971, p. 514) Dr. S. G. Browne (19 February, p. 506) remarked on "a small number of patients treated for an insufficient period of time. . . ." This is relevant to their conclusion that the incidence of erythema nodosum leprosum was similar in two groups of patients, one of which was given clofazimine 100 mg daily and the other dapsone 100 mg daily. Experience at Westfort¹ indicates that while clofazimine in a dose of 100 mg daily does not abolish erythema nodosum leprosum it does decrease its incidence during long-term administration to patients with lepromatous leprosy.

We compared two groups of patients, one of which received dapsone 100 mg three times a week and the other clofazimine 100 mg daily in addition to dapsone 300 mg weekly. All patients had had previous treatment with dapsone alone for an average of eight months and at the start of the trial six out of 16 patients in each group (38%) had some form of reaction, mainly erythema nodosum leprosum. At the end of two and a half years in the trial (that is, after 38 months of antileprosy treatment) there were 15 patients left in the group receiving clofazimine in addition to dapsone and 10 patients in the group receiving dapsone alone (three had been removed from the group on dapsone only at 18 months for severe erythema nodosum leprosum not adequately controlled by corticosteroids, and the others had absconded). Seven of the 15 patients receiving clofazimine and five of the 10 patients in the group on dapsone alone had erythema nodosum leprosum at the end of the trial—that is, an incidence of 27% compared to 50%. If the three patients removed from the trial at 18 months for severe erythema nodosum leprosum are included, the figures are 27% and 60%.

About 30% of all patients with lepromatous and borderline leprosy at Westfort develop erythema nodosum leprosum. Although it may occur early and even in untreated patients, in our experience it usually first presents after an average of 16 months of antileprosy treatment. The lack of a suppressive effect of 100 mg clofazimine daily on erythema nodosum leprosum found by Dr. Karat and colleagues may be due to the fact that few of their patients were treated for long periods. Only 12 of their 23 patients (seven in the clofazimine group and five in the dapsone group) were treated for longer than 15 months.

We have treated more than 100 patients with clofazimine for established erythema nodosum leprosum and our results confirm numerous previous observations that response to the drug depends on an adjustment of the dose to the severity of the re-

action. While a minority of our patients respond to 100 mg daily, most need 300 mg daily and some patients are given as much as 500 mg daily to achieve adequate control of erythema nodosum leprosum.—I am, etc.,

E. J. SCHULZ

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¹ Schulz, E. J., *Leprosy Review*, in press.

Risk with β -Blocking in Bronchial Asthma

SIR,—Adrenergic β -receptor blocking drugs are widely used in the treatment of angina pectoris. Propranolol, the first of these drugs to be introduced into clinical practice, increases airways resistance in asthmatics¹ and the hazards of its use in these patients are well known. We recently observed a case of life-threatening airways obstruction in an asthmatic patient following the ingestion of a single tablet of oxprenolol hydrochloride (Trasicor).

The patient, a 39-year-old barman, had a 30-year history of extrinsic atopic asthma. His symptoms were reasonably well controlled by a salbutamol inhaler used four times daily. He consulted his family doctor on account of episodic aching central chest pain radiating down the medial aspect of his right arm but not closely related to effort. Oxprenolol was prescribed and the patient was instructed to take one tablet (40 mg) at the onset of pain. Eight days later, at work, he experienced an episode of chest pain and took his first tablet of oxprenolol. Within 30 minutes he became acutely breathless and wheezy. He was taken promptly to the casualty department of Aberdeen Royal Infirmary where he was found to have central cyanosis and widespread sibilant rhonchi. Immediate treatment was instituted with oxygen, intravenous aminophylline, and hydrocortisone; his symptoms gradually settled over the following six hours. There was nothing to suggest left ventricular failure and subsequent investigation showed no evidence of myocardial infarction.

All the currently available β -blocking drugs, including propranolol,¹ oxprenolol,² alprenolol,³ and practolol,⁴ have been shown to increase airways obstruction in some asthmatics. The present case further emphasizes the need for extreme caution in the use of any β -receptor adrenergic blocking drug in a patient with airways obstruction.—We are, etc.,

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CRAIG SKINNER

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¹ McNeill, R. S., *Lancet*, 1964, 2, 1101.

² Beumer, H. M., *Pharmacologia Clinica*, 1969, 1, 172.

³ Connolly, C. K., and Batten, J. C., *British Medical Journal*, 1970, 2, 515.

⁴ Palmer, K. N. V., Legge, J. S., Hamilton, W. F. D., and Diamant, M. L., *Lancet*, 1969, 2, 1092.

Treatment for Ovarian Carcinoma

SIR,—Despite the use of maximal surgery, radiotherapy, and cytotoxic drugs, the prognosis for ovarian carcinoma remains poor. Any new form of treatment which can be shown to be of value and which does not preclude the use of any existing form must therefore be welcome.

Recently interest has been aroused in an

injectable progestogen, gestronol hexanoate (Depostat). A group of gynaecologists and radiotherapists has agreed to take part in a co-operative trial to determine the value of this hormone in ovarian carcinoma.

Owing to lack of standard principles of management, the undersigned steering committee has designed the trial so that gestronol hexanoate will be used in randomly chosen cases as an adjunct to whatever treatment the individual investigator's principles of management dictate.

It is hoped that this trial will throw further light on the role of existing modes of therapy as well as that of the hormone. Clinicians who would like further information about this trial are invited to communicate with the full time co-ordinator, Miss J. K. Nesbitt, at the address below. —We are, etc.,

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Lead Poisoning Scandal

SIR,—Dr. M. E. M. Herford (26 February, p. 567) comments adversely on joint appointments as company physician and Factory Inspectorate doctor. He speculates that the perpetuation of "this undesirable practice", under the E.M.A.S. Bill, is to placate the Society of Occupational Medicine.

Whatever may have been its views in the past, the Society of Occupational Medicine at the present time is in no way committed to such joint appointments. Nor has there been any placatory approach by the Department of Employment to the Society in relation to its E.M.A.S. Bill.—I am, etc.,

JOHN ROGAN
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Trial of Clofibrate

SIR,—I have been expecting someone better qualified than I to question the implications of the reports on the use of clofibrate in ischaemic heart disease (25 December 1971, pp. 767 and 775). In general I am concerned about the uncritical application of the theory of probability to heterogeneous populations. The theory is valid for homogeneous groups and can be applied to heterogeneous groups only if numbers suffice to ensure that the multiple relevant variables, which may make each individual unique, are equally represented in control and treated groups. This may be achieved when the relevant factors are few and are known, but may be difficult or impossible when aetiology is uncertain, as in ischaemic heart disease. I am not convinced that this condition has been satisfied in the reports from Newcastle and Scotland. Similar difficulties probably account for 25 years of indecision over the value of anticoagulants,¹ and may be relevant to the disputed findings of the University Group

Diabetes Program study in the United States.²

In the clofibrate trials it is reasonable to expect that any significant benefit will be apparent in the largest group—namely, males not given anticoagulants. There were relatively few females and anticoagulated patients in the trials, and in both groups the causative factors and the course of ischaemic heart disease probably differ from those in uncoagulated males. The records show a notable difference in results for male and female patients, while in the Newcastle trial there was a significant difference in the death rate for all those on anticoagulants (24.6%) compared with those not so treated (13.8%).

The Scottish trial records the higher mean systolic pressure and the higher mean serum cholesterol in the placebo group. In fact for those not on anticoagulants there was a significant excess in the placebo group of males with a systolic blood pressure >140 mm Hg (clofibrate 73, placebo 110; $P<0.01$), and again an excess with a diastolic pressure >90 mm Hg (clofibrate 62, placebo 97; $P<0.01$). There was also a significant difference in the Combined trial among males with a serum cholesterol >260 mg/100 ml (clofibrate 135, placebo 179; $P<0.02$) and particularly for those of this group aged over 50 years (clofibrate 71, placebo 107; $P<0.01$). Of the latter all those who had a previous history of angina, later identified as an important group, were most unevenly distributed (clofibrate 21, placebo 43; $P<0.01$). I do not have comparable data for the Newcastle trial, but the difficulties of eliminating bias even in the case of assessable factors is already apparent. How other factors such as latent diabetes were distributed; how many unknown factors were present; and how all these factors, known and unknown, certainly relevant and possibly relevant, interact together, we cannot tell. Statistical analysis in these circumstances is on a manifestly insecure foundation.

Secondly, I understand it is a principle of statistical method that a trial of this sort is initiated to test a postulate on statistical grounds. The Scottish group record their intention to test the value of reducing raised serum lipids in patients with ischaemic heart disease. No such value was demonstrated. The Newcastle group were looking for any effect on the morbidity and mortality of patients with established disease. There is no evidence that any selective benefit for patients in specified symptom categories was expected.

In the two trials many hundreds of valid comparisons can be drawn between groups differing in respect of age, sex, clofibrate administration, previous history, anticoagulant therapy, etc. It is to be expected, therefore, that there will be thrown up by chance an appreciable number of statistically significant differences between subgroups, with secondary influences on collated groups.

Insofar as analysis of the available data is possible, most of the significant differences recorded in the trials and in the Joint Commentary appear to vanish, if the important group of males not taking anticoagulants is considered separately. In the Scottish trial the rate per 1,200 patient-months for infarcts, fatal and non-fatal, was clofibrate 4.70, placebo 4.30. Similar figures for the Newcastle trial were clofibrate 6.08, placebo 7.71, though these included anticoagulated patients. The results are even less impressive

if the contribution that seems to have been made by patients who withdrew from the trial is excluded. If, as appears, the records of these patients are represented in the results up to the time they withdrew, then exclusion is justified. They were a selected group, in that survival was a condition of withdrawal.

My objections may be illustrated in a composite statement of some of the Newcastle results. Clofibrate provides significant protection against sudden death for patients with a previous history of angina provided they have also had an infarct, and provided those taking anticoagulants are included. Against non-fatal infarction, clofibrate provides significant protection only if those taking anticoagulants are excluded, but now the only subgroup to benefit consists of those patients with angina who have not also had an infarct. It is not difficult to see that something is wrong here.

I believe that conclusions of this sort stem from an uncritical acceptance of chance findings, such as are to be expected in a mass of statistical data derived from significantly biased groups. I certainly would not deny the value of the work done, nor that it may not assist in pushing back a little further the frontiers of darkness. It has not been shown that clofibrate is of no benefit in ischaemic heart disease. But any suggestion that a future similar trial would be unethical or that it would not now be justifiable to withhold clofibrate from a patient with a particular history, I should regard as not supported by adequate evidence.—I am, etc.,

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- ¹ Report of the M.R.C. Working Party, *British Medical Journal*, 1969, 1, 335.
- ² *British Medical Journal*, 1970, 4, 444.

Staffing our Asylums

SIR,—I entirely agree with the statement in your leading article (26 February, p. 523) that "The Health Department should be given credit for having found more money for mental handicap and mental illness in the last two or three years; but the sort of sums needed if the old asylums are to go are unlikely to be forthcoming."

I recently calculated that if we were to stop admissions forthwith, and if the present rates of death and discharge were maintained, the last of the patients now in the Stoke Park Hospital Group would leave us about the year 2040!

At the Annual Conference of the National Association for Mental Health on the 25 February 1972, Sir Keith Joseph said that this and the previous Government were committed to allowing independence to local authorities in determining their health and social service expenditure. I asked Sir Keith whether it was not quite unrealistic to expect local authorities to provide adequate residential accommodation for the mentally subnormal by the target dates in the Command White Paper—*Better Services for the Mentally Handicapped*¹—unless the Government made a specific financial allocation for this purpose, and, therefore, extremely unfair for regional hospital boards to base their plans for chronically deprived hospitals on the assumption that local authorities were, in fact, going to be able to meet these target