in other cases due to the ulcerated nature of the surface of the tumour. We feel, therefore, that a biopsy is required for any cervix which has the clinical appearance of malignancy, despite an initial negative smear.

As Professor McLaren has said, cervical smears from patients with irregular bleeding, in whom body cancer is suspect, are not infrequently negative. We have found, however, that in such circumstances vaginal smears are frequently positive when a cervical scrape is negative, the exfoliated cells having been caught in the vaginal vault. When, therefore, body carcinoma is suspected, both cervical and vaginal smears should be examined before curettage.—I am, etc.,

J. ELIZABETH MACGREGOR.

Department of Midwifery
and Gynaecology,
University of Aberdeen.

Oral Contraceptives and Liver Damage

SIR,—In an article in your journal (15 August, p. 426) Drs. A. Eisalo, P. A. Järvinen, and T. Luukkainen mention that abnormal values of liver-function tests were found in post-menopausal women taking Lyndiol, suggesting a possible hepatic dysfunction due to this oral contraceptive. They believe that the oestrogen component (mestranol) might be the cause of this abnormality.

At the end of their paper the authors write that they also want to study the influence of oral contraceptives on liver function in younger women, in order to be better informed on hepatic function during oral contraception.

As such an investigation has already been made as a part of a larger field-trial in Holland (carried out under my supervision) in which among others the same liver test (S.G.O.T.) as the authors used was employed, our results might be of interest to the readers of your journal.

Starting in February 1962 Conovid (5 mg.) and Lyndiol were given to 500 women in three clinics of the Dutch Planned Parenthood Association (called N.V.S.H.) in a double-blind way, so that neither the patient nor the doctor knew what kind of tablet was given. The results of this trial have been published.^{1,2}

In one of the clinics, at Rotterdam, a more intensive study of liver function was made by evaluating monthly the amount of bilirubin and transaminase (S.G.O.T. test) in the blood of 30 women taking Lyndiol and 30 women taking Conovid. In nearly all these cases the oral contraceptive was given during at least half a year. The results of both groups will be mentioned, as both kinds of pills contain the same oestrogen (mestranol) that Eisalo *et al.* suggest might be blamed for the abnormal results of their tests (Conovid, 0.075 mg. mestranol per tablet; Lyndiol 0.15 mg. per tablet).

The bilirubin content of the blood was always normal, suggesting that there was no sign of a subclinical icterus in any of the cases.

Altogether 342 S.G.O.T. determinations were performed in the laboratory of Dr. Schopman in Rotterdam. In two cases 23 units were found, while in all the other tests the values were less than 20 units. All the results therefore remained well within normal

limits (under 40 units), so that in these healthy young women, aged from 21 to 35 years, no sign of abnormal liver function was found. This is in contrast to the results observed by Eisalo *et al.* in older women, though Lyndiol and Conovid were administered in our investigation for a much longer time—generally during six cycles—than in their study.

In accordance with other investigators who also found a normal hepatic action during medication with Enovid or Conovid,³ we feel, therefore, that there is no reason to believe that oral contraception with either Lyndiol or Conovid will damage the function of the liver in any way.—I am, etc.,

L. I. SWAAB,

Chairman, Medical Board, Dutch F.P.A.
(N.V.S.H.).
Amsterdam, Holland.

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SIR,—The preliminary communications of Dr. A. Eisalo and others (15 August, p. 426) reporting hepatic dysfunction in post-menopausal women treated with a contraceptive drug (Lyndiol) reminded us of a patient treated by us nearly two years ago.

A woman aged 35 years presented to one of us (D.L.P.) on 15 November 1962 with a fever, followed by frequency of micturition, a diffuse maculopapular rash, puffy eyes and conjunctival injection, and albuminuria; a week later she developed herpes labialis, and the next day bile salts in the urine, and on the ninth day clinical jaundice. It was thought that this might be an allergic reaction, the only drug treatment being that she had received four three-week courses of Anovlar as a contraceptive (having had five pregnancies in rapid succession).

She was admitted to hospital on 1 December 1962 on the 14th day of the illness, at which time she had a fever of 99.5° F. (37.5° C.), an almost confluent brownish-pink erythema starting to desquamate, and was clinically jaundiced. The liver was palpable two to three finger-breadths below the costal margin. There were no other abnormal signs.

Liver-function tests: serum bilirubin, 5.9 mg. per 100 ml.; thymol turbidity, 4 units; thymol flocculation, negative; cephalin cholesterol, negative; alkaline phosphatase, 37.8 K.A. units.

Serum transaminases: S.G.O.T. 148 Sigma-Frankel units; S.G.P.T. 260 Sigma-Frankel units.

Blood count: Hb 81%, W.B.C. 7,100, polymorphs 50%, lymphs 44%, monocytes 4%, eosinophils 2%.

Paul-Bunnell, cardiolipin reaction, W.R., Reiter's test, canicola fever: negative.

She recovered steadily and after two weeks was well, free of jaundice, and serum bilirubin was 1.3 mg. per 100 ml.

It is notable that this illness with rash and jaundice was at first thought to be allergic, but that Anovlar was dismissed as the cause. Anovlar tablets contain norethisterone acetate, 4 mg., and ethinyloestradiol 0.5 mg., whereas Dr. Eisalo and his colleagues reported on Lyndiol, of which each tablet contains ethinyloestrenol, 5 mg., and mestranol, 0.15 mg. Anovlar and Lyndiol are therefore similar but different compounds, and our object in briefly reporting this case is to raise the question of whether another substance than mestranol which was implicated by Dr. Eisalo in use as an oral contraceptive might have caused reversible liver damage. It is, of course, possible that the illness and ex-

posure to Anovlar may not have been related, but it seemed to us that we should report the case so that others would be encouraged to look at their cases of jaundice with this in mind.—We are, etc.,

Orsett Hospital,
Grays, Essex.

J. W. FAWCETT.
D. L. PEDERSEN.

The Hydrocephalus Association

SIR,—I was interested to read Dr. R. M. Forrester's letter (5 September, p. 629) on the Hydrocephalus Association, and I have very full sympathy with his feelings about having yet another association and for his plea that the children with hydrocephalus and spina bifida should be accepted by the Spastics Society.

The Spastics Society have been approached on this matter on more than one occasion over the past few years, but, unfortunately, have not been able to take children with hydrocephalus and spina bifida under their wings because of their charter. It was because of this persistent refusal that the parents of hydrocephalic children, and those who look after them, had to take a step to form an association to further the interests of their children. Perhaps it may yet come that when the Hydrocephalus Association is fully established an amalgamation between them and the Spastics Society could be arranged. This would be very much to their mutual benefit.—I am, etc.,

Department of Child Health, JOHN LORBER.
University of Sheffield.

Hormones and Breast Cancer

SIR,—Dr. F. I. R. Martin is to be congratulated on his contribution (8 August, p. 351) to a study which may well be of prime importance in the future of hormone therapy of breast cancer. The study of gonadotrophin-excretion level is of importance, not only as a prognostic guide in the selection of patients for ablative therapy (as stressed by Dr. Martin), but possibly also as a means of understanding the basis of ablative therapy in this disease.

On a prognostic basis Dr. Martin's results suggest that a low gonadotrophin excretion is associated with a poor response to endocrine therapy. His methods of therapy included androgens, anabolic steroids, and corticosteroids, in addition to oophorectomy, adrenalectomy, and hypophysectomy. Segaloff *et al.*¹ had similarly noted an association between low gonadotrophin excretion and poor response to hormone therapy. On the other hand Loraine *et al.*² reported that the baseline gonadotrophin excretion was of no prognostic significance in assessing response to oophorectomy or adrenalectomy in patients with breast cancer. Apart from technical considerations the discrepancy is difficult to explain except on the basis of criteria. Dr. Martin includes subjective relief of pain as a response, and also includes anabolic steroids and corticosteroids among his methods of endocrine therapy.

Observation of the changes in gonadotrophin excretion after ablation therapy may have an even greater significance. Several groups of investigators agree that after oophorectomy or adrenalectomy a higher mean level of gonadotrophin excretion indicates a greater likelihood of clinical remission.³⁻⁵ On the other hand it has been demonstrated

that the changes in urinary-oestrogens excretion after oophorectomy or adrenalectomy cannot be related to clinical benefit.⁶ A possible conclusion is, therefore, that the benefit that follows oophorectomy or adrenalectomy in some patients with breast cancer is due not so much to removal of oestrogen as to the consequent liberation of gonadotrophins that follows such ablation therapy.

In other words breast cancer in the younger woman may not be so much "oestrogen dependent" as "pituitary dependent." There is, of course, other evidence that points to the same conclusion, but I hesitate to repeat this evidence in a letter. I would add only that my suggestion should lead logically to a trial of human pituitary gonadotrophin administration in patients with breast cancer failing to respond to castration. A similar trial was suggested in the treatment of cases showing a low gonadotrophin excretion after adrenalectomy.⁸ The absence of reports of such trials in the literature to date reflects the difficulty of procuring adequate supplies of human pituitary gonadotrophin for therapeutic trial, but I hope that this will be remedied in the near future.—I am, etc.,

Melbourne, Australia. BASIL A. STOLL.

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Drugs for Depression

SIR,—Your leading article (29 August, p. 522) on "Drugs for Depression" requires some comment.

Firstly, you promulgate the "pseudo-scientific" myth that depressions can be divided into endogenous and reactive types, in spite of the formidable researches of Lewis¹ and Garmany.² We³ have reinvestigated this problem in Edinburgh and found only two factors which were clearly discriminatory, severity of depression and history of previous manic episode. We feel, therefore, that using the dichotomy endogenous-reactive as a basis for differing drug therapies is misleading. Your contributor goes on to mention Drinamyl (dexamphetamine and amylobarbitone) as an efficacious agent in the treatment of depressive symptoms occurring in the context of a personality problem. This seems surprising in 1964, when we know that amphetamine is highly addictive⁴ and that it can readily cause toxic psychoses.⁵ Then there is reference to iproniazid as "still the most effective" of the monoamine oxidase inhibitors, without adequate reference to the appreciable mortality from liver damage.⁶ Finally, in the

last paragraph there is the suggestion that nortriptyline has a strong sedative effect, but has "not yet been adequately assessed." I presume, Sir, that your contributor had not had the opportunity of reading the recent issue of the *Scottish Medical Journal* in which our evaluation of nortriptyline is reported.⁷ We found this drug to be more effective, on the sample of depressives treated, than amitriptyline, and also markedly less sedative. In fact, we found nortriptyline to have a quite definite antidepressant or stimulant effect more akin to that of imipramine.

It may seem presumptuous to question your leading article this way, but it will be read by many general practitioners who treat many of their depressive patients themselves and will regard your leader as authoritative. In this field, where the effect of the doctor is often as great as that of the drug, it is not wise to be dogmatic.^{8,9} Nevertheless, it may be justifiable, taking severity of depression as the criterion, to suggest the following rank order of antidepressant drugs. For severe depressions, imipramine is generally accepted to be first choice, and, if our experience proves to be any guide, nortriptyline may well become second choice. For moderate depressive reactions, especially where agitation is prominent, amitriptyline with its marked sedative effect is indicated. For milder depressions, especially where anxiety and phobic symptoms are present, the combination of phenelzine and chlor-diazepoxide is a good treatment regimen.¹⁰ Tranylcypromine may be used in small dosage—that is, 10 mg. b.d.—in special cases, and iproniazid in the very exceptional case, though personally I regard it as too toxic. It is my opinion, and the opinion of many psychiatrists in this region, that amphetamines should never be prescribed for depressive illnesses.—I am, etc.,

A. D. FORREST.

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Morningside, Edinburgh.

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Ampicillin for Typhoid Carriers

SIR,—I read with obvious interest Dr. K. F. Anderson's letter (29 August, p. 571) in which he criticizes my earlier letter on the treatment of typhoid carriers with ampicillin (9 May, p. 1252). His letter raises many points of undoubted interest but I would like to confine myself to a few comments.

I am surprised that Dr. Anderson's experience has been limited to cases in which there was "obvious gall-bladder disease with one or more calculi present."

My experience, in accord with many others, includes a large number of cases in which no such pathology was present. Christie's¹ series of eight faecal carriers included four

with normal functioning gall-bladders and no evidence of stones.

The object of my letter, however, was not to discuss the aetiology and pathology of the carrier state but briefly to report on what seemed, and indeed still seems, to be a very encouraging response to a new antibiotic in patients who had previously resisted all chemotherapy.

Whatever our later investigations into these patients' serology may show in the way of Vi-antigen titres, the fact remains that the excreta of these previously persistent carriers has now remained free of salmonellae for a period of from 18 months to two and a half years, and as such they are unable to trigger off a new outbreak of typhoid fever.

No one would disagree with Dr. Anderson that caution should be exercised before assuming permanent cure of these patients, nor would anyone deny the need for surgery when indicated.

To infer, however, that the reporting of such dramatic changes in the excretion pattern of chronic carriers should await the interpretation of long-term serological investigations of questionable significance reveals surely a failure to appreciate the clinical problem.—I am, etc.,

Prestwich Hospital,
Nr. Manchester.

PATRICIA TROY.

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Pargyline Hydrochloride

SIR,—In your leading article "Drugs for Depression" (29 August, p. 522) you say: "Tranylcypromine (Parnate) is the only monoamine-oxidase inhibitor that is not a hydrazine." As far as antidepressive drugs are concerned this statement is true. We would, however, like to remind you that pargyline hydrochloride (Eutonyl), which is intended for the treatment of hypertension, is also a non-hydrazine monoamine-oxidase inhibitor.

Until the introduction of pargyline hydrochloride monoamine-oxidase inhibitors were mainly intended for use in the treatment of depression, and it is important to remember that here we have an antihypertensive which requires the same precautions as regards cheese, yeast extracts, alcohol, etc. It is possible to avoid these reactions, and for this reason we have made available instruction cards for patients which list the dietary and other restrictions involved.—I am, etc.,

Abbott Laboratories Ltd.,
Queenborough, Kent.

J. S. MUNRO.

Arteriospasm after Ergotamine Tartrate

SIR,—Dr. E. Byrne-Quinn's memorandum (29 August, p. 552) prompts me to report a similar case recently admitted to University College Hospital.

The patient is a 59-year-old woman, admitted 18 months previously with non-thrombocytopenic purpura, the cause for which was obscure. Since then she had had about three attacks of headache accompanied by visual disturbance suggestive of migraine. The last attack began one week before admission. Four days later Cafergot-Q tablets (containing 1 mg. ergotamine tartrate) were prescribed. She took three of