sensitivity of the assay (30 picograms/ml.).

These results contrast with the failure of the plasma corticosteroid levels to respond to insulin or lysine vasopressin in a patient several months after the withdrawal of long-term prednisolone therapy given two to three times per day, in keeping with the findings of Livanou *et al.*³

The details of these cases will be published in due course. Meanwhile it is clear that the theoretical disadvantage of depot tetracosactrin referred to by Drs. Treadwell and Dennis is not a practical reality, at least when it is used in a dosage of 0.5 mg. intramuscularly twice weekly.—We are, etc.,

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- 2 Landon, J., in *Recent Advances in Endocrinology*, 8th ed., p. 240. Ed. V. H. T. James, London, Churchill, 1968.
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Ultrasonic Localization of Perforating Veins

SIR.—Many surgeons are unwilling to make long incisions through poor tissues of limbs which are the seat of severe post-phlebitic changes, because of the frequently encountered difficulties with healing. Yet few would disagree that the detection and obliteration of incompetent perforating veins is an important part of the ideal theoretical treatment. It is well known that incompetent perforating veins not dealt with during operations for varicose veins are a frequent cause of persistent symptoms and recurrent varices. Phlebography is an accepted but not frequently used method of detecting perforating veins.¹ A simply applied clinical test is described below.

The pencil probe of a Parkes model 802 Doppler blood flow velocity detector* is modified by the addition of an easily detachable spring-loaded device to compress the superficial veins in a 2 cm. radius around the tip of the probe (see Fig.). The theoretical considerations of the model 802 Doppler have previously been reported.² Probable sites of incompetent perforating veins are marked on the patient's leg by palpating for fascial defects as advocated by Fegan,³ and the usual anatomical sites of perforators can also be marked. In cases without obvious varicose veins, or with gross fibrosis and oedema which make palpation difficult, the superficial veins can be detected with the Doppler and an examination carried out over their course.

The modified probe is placed vertically over the marked sites and depressed, compressing the superficial veins and bringing the probe itself into light contact with the skin, which is covered with coupling jelly. The examiner now regularly compresses and releases the calf with his free hand while manipulating the probe in various directions. If the probe is over an incompetent perforating vein a distinct to-and-fro motion of

blood in the vein can be heard each time the calf is compressed and released. Noise, presumably from ultrasound reflected from moving tissue planes, is present, but is much coarser than the blowing sound produced by moving venous blood, and the two can be readily distinguished.

This procedure has been carried out on anaesthetized patients on the operating-table. The vessel can then be exposed through a small incision. Incompetence can be demonstrated by retrograde flow before ligation. Alternatively, compression sclerotherapy can be carried out with accurate placement of the sclerosant, the effectiveness of which can be checked at a subsequent examination.

The beam of ultrasound issuing from the tip of the probe is said to be only 1 mm. or so wide, and this allows accurate localization. The method does not demonstrate competent perforating veins, as blood flows only from superficial veins to deep veins and does not return. It is accurate in that false positive results do not occur if the ring is properly depressed and if bony prominences are taken into account, though it cannot, of course, be claimed that no incompetent veins are missed.

This technique has been developed with the help of an Ernest Hart Award from the British Medical Association.

—I am, etc.,

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Renin and Acute Renal Failure

SIR.—The article by Dr. J. J. Brown and his colleagues (31 January, p. 253) is a very interesting and detailed introduction to the proposition that renin may cause renal failure or contribute to it. We are, however, left in suspense with a hypothetical conclusion based on circumstantial evidence. One can try to prove the point experimentally, and there are several avenues open. In any such experiments it would be prudent to view with some deference the verbal and written diatribes of Homer Smith against using rabbits in any renal physiological experi-

ment. I suggest, therefore, one should confine experiments to dogs and so avoid the conflicting results already existing in the literature.

Since renal failure in humans is usually the result of a sudden episode, any theoretical involvement of renin must surely require a sudden flooding of the outer renal circulation with very large quantities of this substance. If so, the amount of renin or angiotensin flooding the renal circulation must maintain exclusion of outer cortical flow for over 1½ hours if warm ischaemia is to cause tubule damage or frank acute tubular necrosis. Alternatively, a large dose of renin or angiotensin must be shown to be immediately and directly toxic to the tubule cells.

The Goldblatt clip on the renal artery experiment does not alter the renal distribution of blood, but reduces its perfusion pressure. At the same time the blood pressure rises, owing presumably to the release of excess renin/angiotensin. There is no evidence that this increased renin is vasoconstrictor to such an extent that the outer cortical vessels become excluded from perfusion. These vessels are still being perfused at a reduced pressure, and there is no evidence that the already reduced glomerular filtration rate leads to tubular damage.

A more physiological method of reducing renal blood flow and perfusion pressure involves Priscol (tolazine hydrochloride). Tolazine was used clinically as a peripheral vasodilator, but it is also a potent renal vasoconstrictor; 25 mg. injected intravenously will vasoconstrict the kidneys of a 22 kg. dog for up to 150 minutes.¹ This effect reduces blood flow and perfusion pressure but does not change distribution. The net effect should stimulate renin production, but no tubule damage has been observed, nor does outer cortical vasoconstriction progress with time. Ten minutes after an injection of tolazine the above vasoconstriction is established, as judged by Thorotrast (thorium dioxide) arteriograms. If now 0.05 mg. Hypertensin (angiotensin) is injected into the renal artery a profound reduction in blood flow occurs with no flow beyond the arcuates. The kidney responds within 15 seconds and becomes anuric. Normal and transplanted kidneys recover from this treatment in about 15 minutes, when urine production is resumed. No evidence of tubular or vascular damage followed the severe but temporary afferent vasoconstriction effected on three successive occasions within an hour.

How large a quantity of renin can suddenly be produced endogenously? Can it ever reach the levels of exogenous angiotensin injected in the above experiment? And if it did, would it not lead to its own shutdown, since the outer cortex is not being perfused at all during a period of 5-10 minutes?

There has been some difficulty in correlating blood pressure, plasma renin activity, and aldosterone secretion during rejection episodes in allotransplanted kidneys.^{2,3} This is not surprising. Rejecting kidney allotransplants frequently provoke hypertension and I naively concluded that this was due to renin release from an ischaemic kidney by a Goldblatt effect.^{1,4} Later on, Starzl⁵ came to the same independent conclusion. The results of recent experiments have forced a change of opinion about the role of renin/angiotensin in the production of rejection hypertension.⁶ Sometimes hypertension is not present during rejection, in both dogs and humans, and this is just as mysterious as when it is present, since ischaemic kidneys are common to both clinical situations. Perhaps a reasonable explanation is that outer cortical flow is completely excluded in those rejections presenting without hypertension.

*Parkes Electronic Laboratory, Beaverton, Oregon. Available in Britain from Instrumentarium Ltd., 28 Manchester Street, London W.1.

Though the renin content of a kidney is stated to be reduced by denervation and steroids (as in kidney allotransplantation presumably) there appears (in a large proportion of rejection episodes) little interference with the mechanism which allows hypertensive states to be reached.

So far as I can determine by experiment, the role of renin in renal failure remains an interesting speculation lacking direct evidence in its support. There is, however, some direct evidence against its primary involvement.—I am, etc.,

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Diarrhoea and Light Therapy in Neonates

SIR,—Several different centres have shown that the maximum level of serum bilirubin in premature infants is significantly lower in those exposed to light therapy.¹ So far as we are aware there has been only one reference² to the occurrence of diarrhoea associated with this treatment.

Recently we have started using an air shield phototherapy unit manufactured to the specifications of Dr. J. F. Lucey.³ In several infants about three hours after starting treatment frequent loose stools were passed, and this continued until the therapy was stopped altogether or the light was turned off for one hour in every four.

We consider that this complication should be more widely known, otherwise an outbreak of acute gastroenteritis may be feared. We are intrigued by this phenomenon and wonder whether any of your readers have noted it and have worked out the aetiology.—We are, etc.,

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Azotaemia Aggravated by Tetracycline

SIR,—I agree with Dr. O. M. Edwards and others (3 January, p. 26) that tetracycline may cause clinical deterioration in patients with any degree of renal insufficiency more often than the reports suggest.

There are many reasons for this lack of reports. Firstly, lack of suspicion, particularly where there is no known renal disease or the non-specific symptoms of anorexia,

nausea, vomiting, etc., can be accounted for by the illness for which the drug was given. Secondly, the previously popular five-day course may have been too short to produce the full effect—if this is so, cases may be expected to increase with the larger courses, and perhaps with newer formulations such as Chymocyclar. Thirdly, there is often considerably difficulty in proving the relation of tetracycline to the rise in urea because immediately pre-tetracycline urea levels are not available. Thus of sixteen cases where it has been highly likely that deterioration was caused by tetracycline in only two were the relevant urea levels known.

The urea curves for these two patients were strikingly similar to those of Westminster Case II (see Figure) and the two

FIG.—74-year-old man admitted with lobar pneumonia. Deteriorated during convalescence.

cases reported by Wray and colleagues,¹ and illustrated some important practical points. Firstly, there is a delay of several days after starting the drug before the increasingly rapid rise of urea begins, so that too early monitoring of the urea may miss the rise and produce a false sense of security. Secondly, there is a further delay after withdrawal of the drug before the equally rapid fall of urea starts. During these days the urea may continue to rise, making it difficult to resist requests for immediate dialysis. It is usually, however, reasonable to wait and see, provided no dangerous complication such as severe hyperkalaemia is present. Thirdly, if the expected fall does not occur this may be due to several reasons, apart from renal disease. The extent of the fluid intake/output imbalance may not have been appreciated if assessed over too short a period and inquiry not made for any early diuresis, etc. Thus a patient may present with oliguria due either to acute renal failure or to dehydration alone. Similarly, gross calorie deficiency is common, particularly after a period of nausea and in postoperative patients who may also be hypercatabolic, and this will keep the urea high. Finally, many of these patients may have been taking high protein, electrolyte-containing food such as Complan in large amounts in spite of the maker's warning, either as outpatients or in hospital, particularly when tube-fed. Complan causes an osmotic diuresis, and, in the absence of adequate fluid intake, dehydration, hyperatraemia, and a raised urea.

Cases obviously at risk are those with renal disease and with diseases likely to be associated with renal insufficiency, such as diabetes mellitus, systemic lupus erythematosus, myelomatosis, etc., and also the el-

derly. It has been found useful to give such patients a note explaining why tetracycline is contraindicated and to ask their family doctors to avoid prescribing it if possible.

It is impracticable to monitor all patients on tetracycline in general practice, but unexpected deterioration should raise the suspicion of underlying renal disease and calls for urea and electrolyte estimations. Abnormal results should lead to immediate withdrawal of the drug and full investigation.

The case shown in the Figure was admitted to Stoke Mandeville Hospital in 1965 under the care of Dr. W. B. Thomson, who diagnosed tetracycline-induced azotaemia.—I am, etc.,

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REFERENCE

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Dermatitis Herpetiformis and Gluten-free Diet

SIR,—Drs. R. Marks and M. W. Whittle rightly say (27 December, p. 772) that we have failed to find improvement in the rash of dermatitis herpetiformis in response to treatment with a gluten-free diet,^{1,2} and indeed our more recent observations provide further evidence for this view.^{3,4} This failure of the rash to respond to gluten withdrawal was seen in patients who over the same period of time showed considerable improvement in their coeliac syndrome. Our observations are not so very different from those of Drs. Marks and Whittle, though the conclusions both they and, on another occasion, Fry *et al.*⁵ draw differ from ours.

The authors point out the difficulties which arise in assessing the result of treatment in a condition which has a fluctuating course and a reported mean duration of four years,⁶ and we believe the apparent "improvement" in the rash in the majority of cases they describe can equally well be attributed to the natural history of the disease. In addition, the fact that the dose of dapsone (mean 144 mg./day and range 50-300 mg./day) taken by their patients before starting the diet is considerably greater than that in our own patients, some of whom are taking as little as 100 mg./week, makes us wonder whether they omitted to establish that the dose of dapsone taken by the patient before as well as after starting the gluten-free diet was in fact the minimal dose required to control the rash. If the minimal effective dose of dapsone was not established before starting the diet this would explain the apparent decrease in dapsone requirements while the patient was on the diet. In any case it may be that the amount of dapsone required to control the rash is not the right way of assessing the effect of the diet on the skin, and that the question we should be asking is, "Is the rash any better when the dapsone is stopped while the patient is taking the diet than while he is eating normal food?" In the patients in whom we have stopped the dapsone in the course of the gluten-free diet we have found the rash to return with the same severity as before treatment was started.³

The debate now centres on the patients who were able to stop dapsone completely