glycaemia.¹ This insulin-induced hypoglycaemia activates the corticotrophin releasing factor—corticotrophin—glucocorticoid axis. This permanent stimulation is afterwards responsible for the steady hypercorticism in obesity.

Glucocorticoids as well as other anti-insulin factors, involve tissue insulin resistance and hyperglycaemia which, by stimulating the β -cells result in their hyperplasia. Thus the chain of pathogenesis of obesity may be shown as follows: β -cells hypersensitivity to carbohydrates—postprandial hyperinsulinism—postprandial hypoglycaemia—hypercorticism—tissue resistance to insulin and hyperglycaemia— β -cell hyperplasia. The energy imbalance with predominant intake is a result of intensive lipogenesis resulting from hyperinsulinism.

Excessive insulin response to glucose load in obese subjects is well known. But for the successful prevention of obesity it is necessary to separate the "pre-obese" subjects. This group consists of the patients with normal weight and excessive insulin response to glucose load.—We are, etc.,

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¹ Draznin, B. N., and Marakhovskii, Yu. Kh., *Voprosy Endocrinologii (Minsk)*, 1973, 5. In press.

Cutaneous Polyarteritis

SIR,—Your leading article (6 January, p. 6) cites Borrie¹ as making a good case for regarding the cutaneous form of polyarteritis nodosa as a distinct clinical entity with a good prognosis, and you report his finding that a large majority of patients with livedo reticularis and nodules and a history of polyarteritis had no evidence of lung or kidney disease, though lesions in muscles and nerves with fever and a raised E.S.R. were rather common. Nevertheless, we saw a patient in whom the cutaneous manifestations of the disease were a mask behind which a multisystemic arteritis insidiously developed over a period of 30 months.

The patient, a man aged 41, was admitted on 17 November 1971 acutely ill with cachexia, fever, extensive muscle wasting in all limbs, sinus tachycardia, and a blood pressure of 200/120 mm Hg. He gave a history of purple macular and nodular lesions first developing in February 1969, when they were confined to the hands and feet, spreading later to the trunk and limbs. After 10 months blueish-purple eruptions with painful ulceration appeared from time to time. From February 1971 he began progressively to lose weight, and in August continuous fever developed. He had been admitted to various hospitals at various times and treated intermittently with small doses of prednisone for Schönlein's purpura. From the start of his illness in 1969 until the end of September 1971 his blood pressure, analysis of urine, E.S.R., and total blood cell count had always been normal. From October 1971 his condition deteriorated rapidly, with loss of appetite, weakness, epigastric pain, and paresis and hypoaesthesia of the legs.

When admitted to our hospital he presented the diagnostic picture of polyarteritis nodosa. There were signs of severe asymmetrical peripheral neuropathy. On the sixth day he developed irreversible haemorrhagic shock and he died. An enormous right perirenal haematoma was found at necropsy. The source of the bleeding could not be discovered. Macroscopically the kidneys were normal. The histology of the renal vessels and of the skin nodules were typical of polyarteritis nodosa and there were extensive throm-

botic and necrotic changes in the renal interlobar and arcuate arteries.

Motor and sensory neurological disorders are essential to the early diagnosis of polyarteritis nodosa.^{3,4} It was only after close questioning that we elicited from our patient that at the start of his illness he had had some joint pains, and in August 1969, six months after his cutaneous eruption first began, he had noticed weakness in his legs, with numbness, tingling, burning, and areas of paraesthesia, and also transitory pain and stiffness of the legs and hands. These were so slight that they were overlooked by both the patient and the doctors who treated him. Clearly any signs of peripheral neuropathy must be carefully looked for in cases of polyarteritis nodosa seemingly limited to one organ or system.—I am, etc.,

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¹ Borrie, P., *British Journal of Dermatology*, 1972, 87, 87.

² Dyk, T., and Piotrowski, M., *Polski Tygodnik Lekarski*, 1972, 27, 1279.

³ Richardson, J., *Connective Tissue Disorders*. Oxford, Blackwell, 1963.

⁴ Dyk, T., in *Internal Diseases*, ed. E. Szczeklik. Warsaw, Panstwowy Zaklad Wydawnictw Lekarskich, 1968.

Fluoride and Osteoporosis

SIR,—In our opinion, the findings of J. Jowsey and her colleagues¹ in treating patients with osteoporosis with fluoride, calcium, and vitamin D, referred to in your leading article (30 December, p. 748), are open to question.

A critical analysis of their paper shows that their 11 patients had histological evidence before treatment of osteomalacia and not of osteoporosis, since their mean osteoid border was significantly wider ($16.0 \mu\text{m} \pm 0.6$) than that of the aged-matched controls ($12.3 \mu\text{m} \pm 0.6$). Furthermore, their estimate of the correct dosage of fluorides (50 mg) is very arbitrary, as may be deduced from their statement that "the administration of less than 45 mg of sodium fluoride daily did not consistently increase bone formation, whereas the administration of 60 mg or more daily produced abnormal bone." If the dose range is so narrow monitoring is obligatory, especially since the patients who might benefit from treatment are of an age at which kidney function is reduced. Maes and colleagues² and Largent³ have shown that chronic renal sclerosis reduces fluoride elimination.

According to Jowsey and her colleagues¹ a 5% increase in bone formation may be expected with a daily dose of 50 mg of sodium fluoride. Since the errors of measurement in quantitative microradiography are about 10% in the same section and 20% in two different sections,⁴ this 5% increase in bone formation found with a dose of 50 mg fluoride falls within the errors of the technique. It would therefore be wrong at this moment to advocate large-scale uncontrolled trials of treatment of osteoporosis with fluoride, calcium, and vitamin D on the basis of the observations of Jowsey and her colleagues.—We are, etc.,

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¹ Jowsey, J., Riggs, B. L., Kelly, P. J., and Hoffman, D. L., *American Journal of Medicine*, 1972, 53, 43.

² Maes, J., Dufaux, J., and Vandenbroucke, J., *Acta Clinica Belgica*, 1960, 15, 65.

³ Largent, E. J., *Fluorosis*. Columbus, Ohio State University Press, 1961.

⁴ Jowsey, J., et al., *Journal of Bone and Joint Surgery*, 1965, 47-A, 785.

Drugs in Infertility

SIR,—Dr. E. W. Barnes and others (27 January, p. 234) consider that their experience with the use of mesterolone in the treatment of eunuchoidal males is at variance with that which I mentioned briefly in my letter (18 November, p. 425). But is there all that much difference? I stated that of five eunuchoids treated with daily doses of 200 mg three failed to show an androgenic response while the other two responded satisfactorily, though for these two the corresponding daily maintenance doses of fluoxymesterone were 10 and 20 mg respectively. I concluded that mesterolone is a weak androgen and I said that, at maintenance dose levels, "suppression of endogenous testosterone production does occur." Perhaps I ought to modify the latter to read "depression of plasma testosterone levels can occur"—which may or may not be the same thing. I made no comment on the effects of mesterolone on urinary luteinizing hormone and follicle-stimulating hormone excretion.

Dr. Barnes and his colleagues observed "good clinical responses" in all four previously untreated eunuchoids given 200 mg of mesterolone daily—though I would not have regarded an "increase in shaving frequency from once to three times per week" as being entirely adequate after up to two years' treatment. A 30% drop in testosterone levels was noted in some of the patients. In a second group of eight patients previously on testosterone therapy, three found the 200-mg dose of mesterolone to be inadequate for maintenance.

I venture to suggest that there is little discrepancy between the Edinburgh findings and my own and that they confirm, rather than refute, the general statement I had made. Mesterolone would seem to have about one-tenth to one-twentieth the potency of fluoxymesterone when used for maintenance therapy in hypogonadal males; does not this justify the description of "weak androgen"?—I am, etc.,

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Potential of Neuroleptics by Catecholamine Inhibitors

SIR,—There is much experimental evidence to support the view that neuroleptics of the phenothiazine or butyrophenone type block central catecholamine receptors.^{1,2} The synthesis and turnover of catecholamines are thereby increased, presumably owing to a receptor-mediated negative feedback mechanism, and the increased turnover seems to result in an increased sensitivity to inhibitors of catecholamine synthesis. Thus in animal experiments in our laboratory Ahlenius and Engel³ found that an inhibitor of tyrosine hydroxylase (the methyl ester HCl of DL- α -methyltyrosine) greatly potentiated the depressant action of haloperidol. In a pilot