cover, or that loose or infected teeth were involved? If the treatment provided was only fillings performed in a sound mouth would the authors consider that the relationship of dental treatment to the onset of the disease might be fortuitous, especially since it was not possible to isolate the causative organisms to give further evidence?

The answer to this question is of great importance in view of the number of patients for whom dental surgeons routinely provide an antibiotic umbrella before the removal of teeth, but not before filling them.—I am, etc.,

Kingston Hospital,
Surrey. R. A. PEEBLES.

Familial Dysautonomia

SIR,—In a recent report Dr. E. Shinebourne and others (14 October, 1967, p. 91) have confirmed[1] that in children with dysautonomia 2.5% methacholine induces miosis of the pupil, whereas no reaction occurs in normals. When an anticholinesterase drug is given the pupil also contracts, indicating that acetylcholine is being synthesized in parasympathetic nerve endings, although the rate may be reduced or its release impaired. These findings indicate a partial parasympathetic denervation phenomenon.

In addition to these studies they describe pupillary responses to ephedrine. In their subject 2% ephedrine failed to elicit mydriasis, despite the fact that controls exhibited a mean increase in pupillary size of 33%. They suggest that partial sympathetic denervation is responsible for the absent response. It has been shown[3] that infused adrenaline induces an exaggerated hypertensive response in persons with familial dysautonomia, suggesting the possibility of sympathetic denervation supersensitivity. However, the fact that the heart rate of the patient with dysautonomia rises during noradrenaline infusion rather than slowing suggests an absence of the vagal reflex consistent with parasympathetic denervation of the iris. Therefore the exaggerated response to exogenous noradrenaline may be failure to oppose the action of the drug rather than to an intrinsic vascular supersensitivity. Furthermore, there is pharmacological evidence for the presence of catecholamine stores in the iris. Cocaine instilled into the conjunctival sac produces an obvious mydriatic response. But the absence of such a response to a 2% solution of ephedrine does suggest that the catecholamine stores may not be easily released. That a release mechanism may indeed be involved is indicated by the finding that in children with dysautonomia the catecholamine content of the adrenal medulla was much greater than in non-dysautonomic children dying of similar diseases. Evidently the latter depleted their glands under stress of disease. It was concluded that the V.M.A.-H.V.A. defect[4] in dysautonomia is probably related to a sensory deficit rather than to abnormal metabolism or stores of catecholamines.

The possibility of defective release from sympathetic nerves is difficult to reconcile with the clinical observation that during moments of excitement children with dysautonomia are capable of showing blood-pressure elevation in the severe hypertensive range. Although the finding of resistance to the mydriatic effect of ephedrine is most intriguing, there is cogent evidence to suggest that catecholamine deficiency is not the cause of the apparent denervation.—I am, etc.,

ALFRED A. SMITH.
New York Medical College,
New York.

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Zinc Sulphate and Bedsores

SIR,—We read with interest Dr. C. Cohen's letter (1 June, p. 561) on the treatment of bedsores with oral zinc sulphate. We certainly agree that further evaluation of the effectiveness of zinc sulphate is required. In collaboration with Dr. T. L. Dormandy and Dr. M. Musa, of the Whittington Hospital, we have been carrying out over the last six months a double blind controlled trial into the effect of oral and local zinc sulphate on the healing rate of pressure sores.

Patients with pressure sores have been randomly placed into three groups. Patients in the first group receive oral zinc sulphate, 200 mg. three times daily, and a placebo solution is applied locally. Those in the second group receive placebo capsules orally, and a 1% solution of zinc sulphate is applied twice daily to the pressure sores. Those in the third group receive both oral and local placebo preparations. Throughout the trial we have borne in mind the importance of assessing the general condition of the patient and of maintaining uniform standards of nursing care—two factors which have a major influence on the rate of healing. All patients have been nursed on large-celled ripple mattresses, and their physical and mental state has been assessed weekly using a scoring system.[1]

The serum and urine zinc levels in our patients have been measured before and weekly during treatment, using the method described by Davies *et al.*[2] These have been compared with the levels in matched control patients. There is a highly significant difference between the mean serum zinc in patients with pressure sores and the controls, the figures being 81 μg./100 ml. and 91 μg./100 ml. respectively.

It is not yet clear whether the use of oral zinc has any advantage over its local application, but it is hoped to publish the results of this trial when it is completed.—We are, etc.,

D. F. ABBOTT.
A. N. EXTON-SMITH.
P. H. MILLARD.
J. M. TEMPERLEY.
St. Pancras Hospital,
London N.W.1.

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Aphthous Ulceration

SIR,—Your correspondent Dr. A. J. Moore (25 May, p. 494) stresses trauma as a cause of aphthous ulcers. Without a doubt trauma can be part of the cause of this troublesome complaint, but it is far from being the sole cause.

An important factor involved must be the change in the resistance to trauma. How else can we explain the freedom from aphthous ulceration which some patients notice only during pregnancy, or the relative freedom in patients while taking oestrogenic anovulants? Does Dr. Moore suggest that the ulceration which some women develop quite regularly in the few days preceding menstruation is due to increased toothbrush trauma at that time? Should such toothbrush trauma not cause gingival ulceration rather than buccal or sublingual ulcers? The observation that aphthous ulcers are rare in the over-60 age group is explained, in my opinion, not by the number of edentulous patients, or by less enthusiastic dental care, but by an increase in the cornification of the mucosa as we age. Aphthous ulcers adjacent to teeth are uncommon, because the gingival mucosa is one of the more keratinized parts of the mouth.

I do not deny that trauma plays a part, but I believe that any advance in our understanding of this condition must come from a study of the defence mechanisms which alter our resistance to trauma.—I am, etc.,

RONALD CARRUTHERS.
Department of Dermatology,
General Hospital,
Launceston, Tasmania.

Aphthous Ulcers and Folate

SIR,—In view of your recent leading articles on aphthous ulcers (20 April, p. 131) and nutritional folate deficiency (18 May, p. 377) the following case may be of interest.

Mr. A. (50 years of age) has a 14-year history of recurrent crops of painful ulcers in the mouth. In 1963 he developed hoarseness due to ulceration adjacent to the larynx, and for a while was treated with prednisone. He had no genital ulcers or uveitis, but was regarded as having an incomplete form of Behçet's disease. He presented at this hospital in January 1968 with pain in the throat, hoarseness, and dysphagia for several months. In addition to scarring and active ulceration of the buccal mucosa, palate, and tongue there was an indurated ulcer extending from the tonsil to the pyriform fossa on the left pharyngeal wall. The right pharyngeal wall was scarred. The right arytenoid was swollen, with the right vocal cord fixed, while another ulcer was seen on the left false cord. There was extensive ulceration and scarring in the postcricoid region. Biopsy of the ulcers was non-specific. A cine barium swallow demonstrated a rigid hypopharynx with spillover into the trachea. He was noted to be anaemic (haemoglobin 10.5 g./100 ml., normochromia, anisocytosis; this had always been normal in previous admissions to other hospitals).

The diagnosis lay between incomplete Behçet's disease and major aphthous ulcers (periadenitis mucosa necrotica recurrens). Treatment with tetracycline mouthwashes, Beta-Corlan pellets, and Adcortyl-A in Orabase produced some relief of pain but little alteration in the appearance of the ulcers. He was discharged on this regimen to be readmitted only three weeks later with an aspiration pneumonia. All his ulcers were unchanged, and there were two fresh ones on his tongue. His haemoglobin had fallen to 6.6 g./100 ml., with M.C.V. 114 cu. μ and M.C.H.C. 29.5%. Marrow picture showed megaloblastic erythropoiesis with poor haemoglobinization despite the presence of abundant iron, consistent with vitamin-B_{12} and/or folate

deficiency, complicated by the anaemia of infection. His serum B_{12} proved to be in the normal range at 300 $\mu\mu$g./ml. and the serum folic acid low at 1.8 mμg./100 ml. Serum iron was also low at 42 μg./100 ml. He was transfused two units of packed cells, placed on Folvite 15 mg. daily, Cytamen 1 mg. three times a week, and Jectofer 1 ampoule daily for five days, and fed by nasogastric tube for a week. Topical ulcer therapy continued as before. His general condition and blood picture responded satisfactorily, but even more gratifying was the effect on his ulcers. Within three weeks all the ulceration had healed completely. Considerable scarring remains, of course, and he still has a very poor voice and pharyngeal spill, but at present he is managing well enough at home by swallowing small amounts.

Two points arise from this case. The first emphasizes the severity of some cases of aphthous ulceration. Should this spillover get worse laryngectomy may be indicated. The second point concerns the role of folic acid. He presumably developed a nutritional folate deficiency because of eating and swallowing difficulty over the years, but such was the speed of his recovery when this was corrected that it is tempting to assume that folate deficiency may be a factor in perpetuating or aggravating stomal ulceration. We would now consider it worth while investigating the serum folate level in patients with severe ulceration which is not responding to routine measures.

We would like to thank Mr. W. S. Lund for permission to publish this case.

—We are, etc.,

E.N.T. Department,
Middlesex Hospital,
London W.1.

B. D. BIRT.
J. H. MATHER.

Side-effects of Vinca Alkaloids

SIR,—Severe constipation associated with the use of vinca alkaloids is known in man.[1] I should like to report here my observations on the effect of vinblastine sulphate (kindly supplied by Dr. J. M. McGuire from Lilly Research Laboratories) in guinea-pigs; they have not so far been described. In these animals the neurotoxic effect of vinblastine seems to be the main cause of death.

To 38 guinea-pigs of both sexes, weighing 200–400 g., divided in several groups, I gave daily, intraperitoneally, vinblastine sulphate in saline in doses ranging from 80 to 200 μg./kg. These doses are innocuous in rats.[2] In order to remove the effect of peritoneal irritation the drug was administered in quantities from 1 to 3 ml. of saline. However, in definite relationship with the dose administered all the animals exhibited after three to seven days a great distension of the abdomen, dying several days thereafter. Opening the abdominal cavity, both post mortem and under light ether anaesthesia, I saw the bowel extremely distended, especially the large gut, which was full of air. The general aspect was of severe ileus paralyticus. There were no changes in distension of the bowel that could be correlated with the amount of solvent used.

Decreased intestinal motility was described by Goldstone[3] after treatment with pentamethonium in a patient whose constipation mimicked an acute intestinal obstruction. I think that in guinea-pigs, as in man, an important side-effect of vinblastine sulphate is the neurotoxic effect, which is mainly manifested in the ganglion-blockade effect and subsequently dramatic paralysis of the gut. Therefore the treatment of constipation after the use of vinca alkaloids should be considered in this light.—I am, etc.,

ADRIAN VLĂDUTIU.
Department of Physiopathology,
Hospital "G. Marinesco,"
Bucharest 8, Romania.

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Safety of Chloral

SIR,—As a general physician I heartily endorse the hope expressed by Dr. A. J. Hawes (8 June, p. 627) in his attempt to restore chloral as a popular hypnotic. Dr. Hawes wonders "if a case of poisoning from an overdose of chloral hydrate has ever been reported." I am not aware of such a report, but note below very brief information regarding the seven patients admitted to this unit in 1967 having taken an overdose of chloral, or an allied preparation.

Preparation	Amount	Effect on Conscious Level
Tricloryl (triclofos)	25 tablets	Slightly drowsy
" "	"Handful" tablets	Slightly drowsy
Chloral and Nepenthe	? amount	Slightly drowsy
Welldorm (dichloralphenazone)	20 tablets	Drowsy
" "	12 tablets	Drowsy
" "	12 tablets	Fully conscious
" "	6 tablets + beer	Fully conscious

There were no effects other than those on the conscious level. These minimal effects from overdosage support the choice of chloral as one hypnotic which can be prescribed for patients at risk from possible self-poisoning.—I am, etc.,

HENRY MATTHEW.
Regional Poisoning Treatment Centre,
Royal Infirmary,
Edinburgh.

Unusual Presentation of Hypernephroma

SIR,—Dr. G. G. M. Woods (13 April, p. 100) describes an unusual presentation of hypernephroma.

This reminds me of a very similar case I saw about 28 years ago, when I was still practising in Umtata, the capital of the Transkei.

The patient was a European spinster, aged then about 40 years. The history was that she had been looked after by a colleague in Queenstown, who had diagnosed an enlarged liver five years previously, in about 1935. This enlargement gave her some upper abdominal discomfort, but otherwise there were no symptoms whatsoever, and in particular she had no renal symptoms.

On examination I found, as did my colleague, that the lower edge of the liver was displaced about 3 in. (7.5 cm.), and therefore I concurred with his diagnosis.

About one and a half years later she returned, this time complaining of severe menorrhagia. On examination she had a large fibroid uterus, and I therefore did a total hysterectomy. At the time of this operation I thought I would also palpate the liver to see what was causing its enlargement, and to my horror I discovered that the liver was not enlarged but was merely displaced downwards by a very large tumour in the upper pole of the right kidney, which had grown in between the diaphragm and the right lobe of the liver, and in this way displaced the latter downwards. A month later I did a right-sided nephrectomy and found a hypernephroma or adenocarcinoma of the kidney the size of a child's rugby ball. The diagnosis was confirmed by the laboratory.

A few months ago she wrote to me and said that she was now old and ugly, and, as I was the cause of her still being alive, would I recommend her to a good plastic surgeon for a face-lift. In other words, she was extremely well.

The two interesting points here are the complete absence of any renal symptomatology and the displacement of the liver, mimicking hepatomegaly, and the fact that 28 years after surgery there are no signs or symptoms of secondaries. In fact she must have had this tumour for quite a few years before I ever saw her, because already at that stage the liver was displaced considerably, proving again, as we know, that the prognosis of hypernephroma is most unpredictable.—I am, etc.,

Cape Town. J. D. JOUBERT.

Paracervical Block with Bupivacaine

SIR,—Mr. F. C. R. Picton's comments (1 June, p. 561) on Mr. D. H. Gudgeon's article (18 May, p. 403) prompt me to report our own experience of 25 cases of paracervical block with bupivacaine 0.5%, which include one stillbirth.

Using 10 ml. of 0.5% bupivacaine with adrenaline 1:200,000 we have obtained satisfactory and prolonged analgesia in 70% of cases. In two cases there was significant slowing of the foetal heart within 30–45 minutes of the paracervical block, and in one of these the foetal heart sounds disappeared. Eleven hours later normal delivery of a fresh stillborn baby weighing 8 lb. 5 oz. (3.8 kg.) took place. A slightly infarcted placenta weighing 1 lb. 9 oz. (750 g.) followed. Necropsy showed areas of intrapulmonary haemorrhage scattered through the substance of the lung, but no other abnormality.

This patient had a slight degree of toxaemia (B.P. 130/90, urine normal) and was 10 days overdue, so that placental insufficiency was a possibility. Even so, we are not convinced that the paracervical block with bupivacaine and adrenaline was not a factor, and we support Mr. Picton's words of caution.—I am, etc.,

D. B. WHITEHOUSE.
Maelor General Hospital,
Wrexham.

SIR,—The discomforts of labour can be promptly relieved by paracervical block (18 May, p. 403), but I believe that excessive amounts of local anaesthetics are injected by many obstetricians. I have noticed that it is useful and perhaps best to inject at four points, two on each side of the cervix—namely, 3, 4, 8, and 9 o'clock. The injections should not be made deeply. It serves well to inject in the sulcus where the cervical and vaginal mucosa meet—achieving virtually a submucosal injection. Using bupivacaine 0.25% with adrenaline 1 in 400,000 it should not be necessary to use more than a total