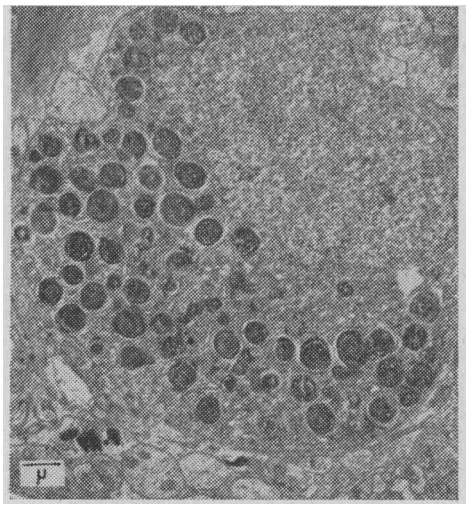
revealed a characteristic alteration of the ganglion cells with many intracytoplasmic membranous structures which are possibly phospholipids (see Figure). The close morphological resemblance between these inclusions and those described in amaurotic familial idiocy is apparent when comparing the electronmicrograph of a human cerebral ganglion



Electronmicrograph of rat ganglion cell from a chloroquine-treated hooded rat (100 mg./kg. daily for 12 months). The cytoplasm contains many membranous structures.

cell in Tay–Sachs disease[5] with our own observation. The striking similarity between the two entities at both the macroscopic and ultrastructural levels suggests the possibility of common features in the pathogenesis of these specific lesions.—We are, etc.,

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Children with Asthma

SIR,—Dr. B. Dalton (30 March, p. 838) advocates the early use of steroids in the treatment of asthma which may be "psychologically determined" in children. Dr. Anne Tothill (p. 837) suggests that the action of isoprenaline may be disadvantageously modified in states of anxiety, and notes that it is not known if it is altered when given with steroids. Dr. M. J. Greenberg (p. 838) suggests that the use of disodium aromoglycate (Intal) may assist reduction of dosage of prednisone.

I should like to comment on those letters as a result of my experience as a psychiatrist working with a paediatric team in a special clinic for severely ill asthmatic children, many of whom are treated with steroids because they have failed to respond to all other forms of treatment. During a three-year period 32 children under 13 years of age received 5 mg. prednisone twice daily. At the start of our survey I might have been tempted, in agreement with Dr. Dalton, to advocate the early use of steroids in those asthmatic children who showed emotional disturbance, as it was notoriously difficult to get parents to accept psychotherapy for them. The initial response of the whole group of 32 children on prednisone was excellent, and those children who were obviously emotionally disturbed responded as well as the rest of the group. Physical symptoms abated, reactive anxiety disappeared, and long-standing symptoms of emotional disturbance caused less distress than before treatment. The children were not distressed by side-effects of prednisone and developed no replacement symptoms.

Unfortunately a minority failed to sustain this improvement. Of course, physical determinants are of critical importance, but some categories of psychological disturbance were prominent in the case histories of those who failed to sustain a good response. Eleven out of 32 children became dependent on maintained use of steroids, and five of those were among those whose emotional disturbance appeared to play a decisive role in the severity of their asthmatic condition. In four other children personality development showed modifications in character organization, often socially acceptable, but clinically disadvantageous when viewed in relationship to the perpetuation of the asthmatic wheeze and its recurrence during steroid withdrawal. It is possible that this group shows most clearly the complexity of relationship between experience of eczema and asthma, psychological modification of the personality, and response to treatment by steroids.

Three children subsequently died, including two of these severely emotionally disturbed children. We suspect that all three used aerosols excessively during the period of great anxiety which preceded their death. Hence my interest in Dr. A. Tothill's and Dr. M. J. Greenberg's letters. We noted the high incidence of dependency upon comfort habits and failure to resolve infantile dependencies on the mother. These psychological problems were reactivated during the withdrawal stage, and the children became acutely distressed if forbidden to use their inhalers. Research into the safety of these is essential. I suggest that physicians and psychiatrists should co-operate and explore all methods of treatment before resorting to steroids. But if these become necessary they can provide a "breathing space" in which renewed efforts can be made to tackle psychological and physical problems and modify dependency on the use of aerosols.

The cases reported are part of a study conducted by Dr. A. P. Norman at the Hospital for Sick Children between 1961 and 1964.
—I am, etc.,

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Deaths from Asthma

SIR,—Your correspondent Dr. Anne U. Tothill (30 March, p. 837) suggests that the bronchodilator action of isoprenaline could be reversed to bronchoconstriction in asthmatic patients using excessive amounts of this catecholamine. Further, the bronchodilator action of adrenaline secreted during an asthmatic attack might induce bronchospasm in the presence of excess isoprenaline. We have studied the interaction of catecholamines on bronchial smooth muscle in the anaesthetized guinea-pig measuring bronchoconstriction and bronchodilatation with a transducer system. A full account of our experiments will be published elsewhere at a later date, but in the meantime one of the findings is of relevance to Dr. Tothill's point.

The bronchodilator effect of adrenaline was measured as reduction of the bronchoconstriction produced by histamine. Injection of either adrenaline or isoprenaline 20 seconds before the injection of histamine reduced the histamine bronchospasm. Infusions of either catecholamine also reduced histamine bronchospasm. If the injections of one catecholamine were repeated during an infusion of the other the effects of the two catecholamines in reducing histamine bronchospasm were additive. Even though the infusions were prolonged the bronchodilator effects of injections persisted. This is in contrast with the effects of injections on the cardiovascular system during infusions: the tachycardia and the effects on blood pressure of injections of isoprenaline, adrenaline, and orciprenaline were reduced or abolished during the infusion of any one of these drugs.[1] In fact the depressor effects of injections of isoprenaline or of low doses of adrenaline were reversed by infusions. However, no reversal of the bronchodilator actions of adrenaline or isoprenaline occurred during infusions. From these findings it is clear that interactions of drugs on one system do not necessarily apply to another.—We are, etc.,

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REFERENCE

1 Atkinson, J. M., and Rand, M. J., *Brit. med. J.*, 1967, **3**, 239.

SIR,—As a postscript to the lengthy correspondence (6 April, p. 50 and others) on this topic, we should like to make a brief comment on the type of cardiac arrest we have observed in patients with status asthmaticus, and on the treatment of this complication. It is widely assumed that cardiac arrest in status asthmaticus is usually due to ventricular fibrillation, and this could conceivably be the main cause of death in those patients who die in their homes, and in whom ventricular fibrillation may have been induced by the excessive self-administration of isoprenaline. In this unit, however, ventricular fibrillation has been responsible for cardiac arrest in only one of the four inpatients with status asthmaticus who have developed this complication, and the patient was an elderly man who may have had an inadequate coronary circulation. Electrocardiographic recordings showed that the cardiac arrest in the other three patients was due to ventricular asystole, preceded by progressive bradycardia, and we suspect that this may be a more frequent cause of cardiac arrest in status asthmaticus than ventricular fibrillation, particularly in hospital inpatients, who are usually spared the potential hazards of adrenaline and isoprenaline.

In our first case of cardiac arrest caused by ventricular asystole external cardiac

massage failed to produce a palpable femoral pulse, and we assumed that the reason for this was that the grossly over-distended lungs cushioned the pressure applied to the anterior chest wall, and prevented it from being transmitted to the heart. In the next two cases external cardiac massage was similarly ineffective, but open massage immediately produced a palpable femoral pulse and was rapidly followed by a restoration of spontaneous cardiac pulsation in sinus rhythm. Unfortunately, in one case open cardiac massage was not started in time to prevent irreparable cerebral damage.

Open cardiac massage may seem a formidable undertaking, particularly to a physician, but it is in fact a simple procedure, and in almost every hospital the services of a surgeon can readily be obtained to close the wound.

In the light of our recent experience, which is happily not extensive, we now take the view that when a patient with status asthmaticus develops cardiac arrest in hospital and this is shown to be due to ventricular asystole the proper course is to undertake open cardiac massage without delay.—We are, etc.,

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Neoplasia after Ureterosigmoidostomy

SIR,—The report of two further examples of neoplasia of the colon after ureterosigmoidostomy (30 December 1967, p. 783) prompts me to record two cases which have been seen in this hospital.

A 53-year-old man underwent total cystectomy and bilateral ureterosigmoidostomies (by Grey Turner's method) for a stage II moderately well differentiated transitional-cell carcinoma of the bladder in May 1965. Twelve months later he developed rectal bleeding, and, since he also had bleeding per urethram, tumour recurrences were suspected. No masses were palpable, however, and sigmoidoscopy revealed granular erythematous rectal mucosa around the right ureteric orifice, which appeared to be prolapsed. Biopsies of this mucosa were reported as showing inflammatory granulation tissue lined with rectal mucosa. He continued to bleed per rectum intermittently but had no further urethral bleeding. In December 1966 he developed a pain in the right loin. Intravenous pyelograms in July and December 1966 showed increasing dilatation of the right ureter and renal pelvis, and there was an opacity overlying the right side of the sacrum consistent with a ureteric calculus. It was decided to explore the right ureterosigmoid anastomosis. At operation an irregular polypus was found surrounding the ureteric stoma. This was excised and the ureteric mucosa was resutured to the colonic mucosa. A ureteric catheter passed easily up the right ureter and no calculus was found. The histology report on the specimen was: "The section shows a benign polyp of the rectum with hyperplastic glands in an oedematous and vascular stroma. There is a marked inflammatory reaction in some areas but no evidence of malignancy."

The second case was a 10-year-old boy who had had bilateral ureterosigmoidostomies performed (by Grey Turner's method) in August 1960 as the first stage of treatment for an ectopia vesicae. From that time he remained well and showed normal physical development. He had left and right inguinal herniotomies performed in 1961 and 1962 respectively, and the second stage of treatment for his ectopia vesicae was carried out later in 1962. In December 1967 he began vomiting in the mornings, and his mother noticed that his bowel motions appeared to contain blood. He had been taking a potassium and alkali mixture regularly since his first operation. On rectal examination there was a polypoid lesion palpable on the right side. His blood urea was 72 mg./100 ml., and his serum electrolytes showed a mild metabolic acidosis. An intravenous pyelogram showed dilatation of the right ureter and renal pelvis, but no excretion was obtained from the left side. Sigmoidoscopy under general anaesthetic revealed a red polypoid lesion on the right side of the rectum at 10 cm. The ureteric orifice could not be identified, and an injection of indigo-carmine also failed to demonstrate its position. The polypus was removed with a diathermy snare. The histology report on the specimen was: "The section shows granulation tissue covered by transitional epithelium (which is very oedematous in some areas) and rectal mucosa, with distended cysts and much chronic inflammatory reaction." He is still being investigated.

In both these patients the lesions showed a marked inflammatory reaction—possibly due to an irritant in the urine. The first lesion was a benign neoplasm, but the second was probably a prolapsed ureteric orifice. As with most of the previously reported cases, both these patients presented with rectal bleeding and evidence of ureteric obstruction, again emphasizing the importance of life-long follow-up of all patients with uretero-sigmoidostomies.

Both patients were in the care of Mr. H. K. Vernon, and the pathology reports were by Dr. G. T. Allen.

—I am, etc.,

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Normal Serum Folate

SIR,—The paper by Dr. A. V. Hoffbrand and others (13 April, p. 71) raises the problem of defining the normal range for any laboratory estimation. In their series of controls 38% fall below their quoted lower limit of normal. It seems that either their control subjects were exceptional or that the lower limit of normal is in fact set at too high a figure. This latter possibility is borne out by a study of a number of recent papers in the *British Medical Journal*, all of which quote a normal range, or imply it, setting as the lower limit a figure below that of the M.R.C. Group. Modifications of technique and selective groups of patients and controls might account for some of the variation, but there seems to us a case for an alteration to the normal range.—We are, etc.,

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Planned Family Planning

SIR,—I read with interest your leading article on planned family planning (4 May, p. 258), as it emphasizes the conviction I have long held that no postnatal examination is complete without a discussion of contraception. I would like to suggest that this is relevant not only in the underdeveloped countries and among the poor and uneducated but applies equally to every postpartum patient in every country. Few women wish to bear their children at intervals of less than 18 months or so. The resumption of anxiety-free sexual intercourse is a factor of importance in the maintenance of family health and contentment.

In her early years of child-bearing a woman retains the feeling that the number and spacing of her children is a matter of her own choice and decision. It is at this time that she needs, and is likely to profit from, contraceptive advice. As unplanned pregnancy follows unplanned pregnancy, apparently at the will of God, fate, or husband, she is robbed of the basic right of self-determination and drawn into the state of hopeless helplessness which one sees so often in the mothers of overlarge families. The intrauterine devices enable us to help those who have the intention but not the will-power.

The time for a discussion about birth control is not after the sixth or the eleventh confinement but after the first.—I am, etc.,

Nottingham. ALEXANDRA TOBERT.

Royal Malady

SIR,—Amid the great interest stirred up by the two articles of Dr. Ida Macalpine and her colleagues (6 January, p. 7, and 13 January, p. 109) on the royal malady may I be allowed to add another letter to the numerous ones already published?

I was, as were other competent French colleagues, highly impressed by the gigantic work which has led the authors to the conclusion of the possibility of variegate porphyria in the Royal Houses of Stuart, Hanover, and Prussia. This conclusion, if it is confirmed, is indeed of particular importance from both the medical and historical points of view. I think the authors deserve congratulation and encouragement to undertake further study of this enthralling subject. To my great surprise most of the criticisms published in the *B.M.J.* seem to have been written with the opposite intention, one might even say pointedly so.

You have already published the reply of the authors of the original papers on the royal malady (16 March, p. 705). Therefore it is unnecessary for me to enter into details of the discussion. I should like to add only that the arguments of the contradictors, if they were criticized with the same "good will" as they themselves display, could also be refuted point by point. Medical science knows no absolute rules and does not permit peremptory statements. My great personal experience in the field of porphyria makes this remark particularly pertinent. Some of the assertions expressed by the critics of Dr. Macalpine and her colleagues seem too dictatorial, such as ". . . a total faecal porphyrin concentration of less than 200 μg./g. dry weight . . . would virtually exclude the diagnosis" (30 March, p. 841). Or "urine in an attack of either form of porphyria is usually of normal colour when freshly passed" (13 April, p. 118). On the other hand, the diagnostic value of the relatively low faecal level of X porphyrin (15.6 μg./g. dry weight) in Case B is significant as a detailed work of Professor Rimington and colleagues will clearly show (in press).

It seems indispensable to provide further evidence to substantiate the diagnosis of the royal malady. Dr. Macalpine and her colleagues are seeking this, despite great diffi-