There are few reports of acute cerebellar ataxia presenting in adults and it is of interest that Brumlik and Means³ describe two American cases showing "lightening eye movements, peculiar shuddering tremor and cerebellar ataxia."

It is tempting to postulate that encephalitis tremens, a benign epidemic form of acute cerebellar ataxia with R.I.M.E.L. limited geographically to a region of West Africa rain forest, might represent an abor virus encephalitis involving the brainstem. However, such an assumption awaits investigation.—I am, etc.,

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¹ Wright, J., and Morley, D. C., *Lancet*, 1958, 1, 871.

² Personal study while in receipt of Leverhulme Travel Scholarship, 1968.

³ Brumlik, J., and Means, E. D., *Brain*, 1969, 92, 157.

Oxytocin Release by Infused Prostaglandin

SIR,—Dr. Arnold Gillespie and others, results on oxytocin release by infused prostaglandins (26 February, p. 543) are very interesting, but I feel that though the possibility cannot be excluded not enough evidence was provided to allow the conclusion that administered prostaglandins act directly on the pituitary to release oxytocin.

No peripheral oxytocin was detected in one patient in whom prostaglandins did not stimulate uterine activity. This could imply not only that direct prostaglandin-induced oxytocin release from the pituitary is required to enhance uterine activity when administering exogenous prostaglandins, but that prostaglandin-induced uterine contractions might indirectly stimulate the pituitary, even though this may be by release of further amounts of prostaglandin.

Amounts of oxytocin found in prostaglandin-induced labours were similar to those found in the late first stage of spontaneous labour, and seem to indicate little difference in pituitary involvement in these two situations. The observed oxytocin release in males and females could also arise indirectly from one of the many known pharmacological actions of prostaglandins—for example, on renal and intestinal systems.

As further evidence for posterior-pituitary involvement in the action of prostaglandins they cite investigations^{1,2} showing that spontaneous and prostaglandin-induced contractions can be inhibited by ethanol whereas exogenous oxytocin-induced contractions are not. This assumes that spontaneous contractions are the direct result of endogenous oxytocin release, which may not be so. Indeed one might hypothesize from this evidence that it is endogenous prostaglandin release that is effecting uterine contractions in spontaneous labour. Mantell and Liggins³ have shown that ethanol can reduce exogenous oxytocin-induced contractions, and therefore the use of ethanol to define the role of prostaglandins and oxytocin in the control of uterine activity must be viewed with some caution.—I am, etc.,

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¹ Fuchs, F., Fuchs, A.-R., Poblete, V. F., and Risk, A., *American Journal of Obstetrics and Gynecology*, 1967, 99, 627.

² Karim, S. M. M., and Sharma, S. D., *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1971, 78, 251.

³ Mantell, C. D., and Liggins, G. C., *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1970, 77, 976.

Genetic Counselling

SIR,—The table quoted by Professor C. A. Clarke (4 March, p. 606) from Redding and Hirschhorn gives a threefold increased risk of a subsequent sib being affected by Down's syndrome throughout the maternal age range. This is in fact the order of the overall increased risk to a mother who has had one affected child irrespective of her age or the type of chromosome anomaly.¹ But Carter and Evans² showed that most of the increased risk is due to balanced translocation or other factors than maternal age. A mother of a child with trisomy 21, proper, where both parents have a normal chromosome complement, has only a very slightly increased risk above the appropriate to her age. Thus a mother aged 35 years or more at the birth of her first affected child has approximately the same risk of having a second child with Down's syndrome as other members of her age group.—I am, etc.,

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Queen Mary's Hospital for Children,
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¹ Berg, J. M., and Kirkman, B. H., *Archives of Disease in Childhood*, 1961, 36, 645.

² Carter, C. O., and Evans, K. A., *Lancet*, 1961, 2, 785.

Irritable or Irritated Bowel

SIR,—Your leader on the "Irritable Bowel Syndrome" (22 January, p. 197) is an excellent summary of the confusion that has grown up around this symptom complex, which is so ill-defined that one wonders if it really exists.

Everyone is agreed that the function of the intestine is disturbed, and that as yet no structural abnormality has been demonstrated to account for the very genuine symptoms attributed to an irritable bowel. As there is no evidence that the bowel is intrinsically abnormal, it is a pity that the title of this leader perpetuates the assumption that the intestine is primarily at fault. Perhaps the cause of these symptoms should be sought elsewhere.

There is a growing body of evidence which shows that our modern Western diet is abnormal and that this causes several diseases which have appeared on the clinical scene in this century.^{1,3} One of these diseases is diverticulosis of the colon, which has been said by some to be connected with the "irritable bowel syndrome." Certainly, both conditions are common in Western nations and almost unknown in rural Africans.⁴ It is also true that symptoms ranging from vague dyspepsia, heartburn, anorexia, nausea, distention, fullness, and flatulence to generalized abdominal aching and severe colic are common both to diverticulosis and to the irritable bowel syndrome. Furthermore, both may be associated with bowel habits which may vary from constipation to episodes of diarrhoea or to the frequent passing of small hard stools.

In the case of diverticulosis, these symptoms are not caused by the diverticula because they can be relieved or abolished in

85% of patients merely by replacing the cereal fibre that is lacking in our modern diet. This is done by adding unprocessed bran to the food and reducing the intake of refined sugar.^{5,6} Over the last five years, it has been my experience that a high fibre/low sugar diet relieves or abolishes these very same symptoms in patients who do not have diverticula and in whom no abnormality of the intestine has been demonstrated. Consequently, I believe that these symptoms are often caused by an intestine that is struggling with our modern fibre-deficient diet.

None of the observations recorded in your leading article is inconsistent with the theory that these symptoms are caused by a normal bowel whose function is disturbed by its having to cope with an altered environment. This environment changed dramatically when the refining of carbohydrates became widespread only a century ago. The addition of fibre in the form of unprocessed bran in a quantity sufficient to render the stools soft and passed without straining will relieve these symptoms in most patients. The rural African passes soft bulky stools and does not suffer from diverticulosis or from an irritable bowel. In countries where the "irritable bowel syndrome" is common, the diet is so fibre-deficient that it causes the colon to rupture itself so that diverticula appear. If the bowel is being subjected to such an abnormal diet, is it fair to refer to the "irritable" bowel syndrome? Surely it would be wiser to refer to the "irritated" bowel syndrome.

The term irritable bowel syndrome implies that the design or construction of the intestine is intrinsically wrong and it cannot cope with the normal stresses of everyday life. Can this really be so in over half the patients who attend our clinics? It seems more likely that, owing to evolution and natural selection, their bowels are normal but their symptoms are caused by the food they eat. I am, etc.,

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¹ Cleave, T. L., Campbell, G. D., and Painter, N. S., *Diabetes, Coronary Thrombosis and the Saccharine Disease*, 2nd edn. Bristol, J. Wright, 1969.

² Painter, N. S., and Burkitt, D. P., *British Medical Journal*, 1971, 2, 450.

³ Burkitt, D. P., *Lancet*, 1970, 2, 1237.

⁴ Trowell, H. C., *Non-infective Diseases in Africa*, London, Arnold, 1960.

⁵ Painter, N. S., *British Medical Journal*, 1971, 2, 156.

⁶ Painter, N. S., Almeida, A. Z., and Colebourne, K. W., *British Medical Journal*, 1972, in press.

Vasodilating Action of L-dopa

SIR,—The studies of Spiers and Calne¹ and Spiers² show that dopa and dopamine have a noradrenaline-liberating action at the sympathetic nerve endings with depletion of stores. Both substances are also metabolic precursors of adrenaline and noradrenaline. In order to investigate a possible peripheral vasodilating action of L-dopa we have treated a group of 10 patients affected by an atherosclerotic obstructive arterial disease of the lower limbs for more than two years.

L-dopa was administered in increasing dosage from 375 mg/day to a maximum of 3,000 mg/day. All patients were treated for a month and no other drug was administered. Rheographic registrations³ were performed before, during, and after treatment. At the end of a month, three patients did not show any benefit. Seven patients showed subjective

improvement as demonstrated by reduction or in some cases disappearance of spontaneous pain in walking (so much so that after many years two patients were able to go upstairs without pause).

The rheographic tracing was not modified in one case; in six others it showed an improvement both in baseline conditions and after trinitrin.

More prolonged and extended trial is needed to confirm the preliminary observations.—We are, etc.,

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¹ Calne, D. B., Spiers, A. S. D., Stern, G. M., Laurence, D. R., and Armitage, P., *Lancet*, 1969, 2, 973.

² Calne, D. B., Brennan, J., Spiers, A. S. D., and Stern, G. M., *British Medical Journal*, 1970, 1, 474.

³ Nyboer, J., *Circulation*, 1950, 2, 811.

Cancer, F.D.P., and Radiotherapy

SIR,—Your leading article "Fibrin and Cancer" (11 December, p. 641) is a welcome survey of our knowledge in this field. Owing to the coagulative and fibrinolytic properties of malignant tumours fibrin degradation products (F.D.P.) may occur in the blood in patients with such neoplasms. We recently reported (20 November 1971, p. 458) the finding of F.D.P. in as many as 72% of women with malignant ovarian tumours.

We have since had the opportunity of observing some cases of recurrent malignant tumours of the ovary in which the F.D.P. in the blood disappeared after radiological treatment. An illustrative case is reported below.

A girl born in 1953 was subjected to right-sided salpingoophorectomy in June 1969 because of an ovarian androblastoma of uncertain degree of malignancy. Six months later she was re-admitted to hospital because of a large palpable recurrence. Analysis revealed F.D.P. in a concentration of 100 $\mu\text{g}/\text{ml}$. After radiotherapy alone the abdominal mass was no longer palpable and F.D.P. were no longer demonstrable. In June 1970 a new recurrence was diagnosed and the F.D.P. concentration was found to be 300 $\mu\text{g}/\text{ml}$. After irradiation and surgical excision of all visible malignant tissue the F.D.P. disappeared. No F.D.P. were afterwards demonstrable until August 1971, when a third recurrence was detected. Despite reoperation, radiation, and treatment with cytotoxic drugs the tumour grew rapidly, and the patient died in January 1972. The F.D.P. were then 50 $\mu\text{g}/\text{ml}$.

Thus every recurrence was accompanied by the appearance of F.D.P. in the blood. The first recurrence responded well to radiation alone and the F.D.P. disappeared. The symptoms and the F.D.P. disappeared also after surgical and radiological treatment of the second recurrence. The third recurrence was fatal.

It has recently been shown in organ culture studies that the fibrinolytic activity of tumours varies with their vascularity.¹ Irradiation of tumours damages their vessels,² probably with inactivation of the endothelial cells that synthesize the fibrinolytic enzyme. If so, this would explain the disappearance of F.D.P.

We have also regularly found that the

F.D.P. temporarily increases about three to four weeks after the beginning of irradiation of ovarian carcinoma. This increase might be explained by degeneration of the tumour by the radiation with entry of thromboplastic substances into the bloodstream.—We are, etc.,

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¹ Björlin, G., Pandolfi, M., and Astedt, B., *Experientia*, in press.

² Errera, M., and Forssberg, A. G., *Mechanisms in Radiobiology*, vol. 2, p. 153. New York, Academic Press, 1960.

Intravenous Glucagon

SIR,—Dr. J. R. Condon and others (5 February, p. 376) say that the only alternative drug to glucagon acting over a short period in Paget's disease is mithramycin. We have noted similar effects with actinomycin D on RNA inhibition¹ in the same journal on the next page to that of Dr. Condon and colleagues' article about mithramycin.²

We have now shown in subsequent studies³ that the effects of these two agents are quite similar. In addition, we find that relief of symptoms can be maintained by weekly dosage of mithramycin or actinomycin D at dosage which does not cause marrow depression or hepatocellular drainage.—I am, etc.,

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¹ Fennelly, J. J., and Groarke, J. F., *British Medical Journal*, 1971, 1, 423.

² Condon, J. R., et al., *British Medical Journal*, 1971, 1, 421.

³ Fennelly, J. J., *Irish Journal of Medical Service*, 1971, 140, 431.

Halo Naevus—a Frustrated Malignant Melanoma?

SIR,—The same antibodies thought to be specific against the cytoplasm of malignant melanoma have been discovered circulating in all nine patients with a halo naevus. This is a pigmented mole that becomes surrounded by a circular area of depigmented skin during its spontaneous resolution. We postulate that these naevi, always considered benign, may represent the successful rejection phase of malignant melanoma. It is known that rarely melanomas do resolve, sometimes accompanied by halo formation.

During the halo naevus phase of its spontaneous remission a pigmented mole becomes invaded by a massive infiltrate of lymphocytes—signs usually taken to indicate an immune response. This self-healing melanocytic naevus has long been the subject of speculation concerning its pathogenesis and significance.^{1,2}

Recent immunological studies^{3,4} in patients with malignant melanoma have shown the presence of humoral antibodies directed against the plasma membrane and the cytoplasm of the tumour. The cytoplasmic antigen is common to all malignant melanomas: its corresponding antibody is found in early localized malignant melanoma and cross-reacts with the tumour cells of other melanoma patients. It was decided therefore to exploit this situation of a common cross-reacting cytoplasmic antigen to study sera from patients with a variety of skin tumours and pigmented naevi. Sera (diluted 1 in 4) from patients were tested for antibodies by the indirect immunofluorescent technique, incorporating a number of refinements.⁵ The

FIG 1. Clinical photograph (ultraviolet) of halo naevus on back.

fluorescence was read as positive only if over 25% of the malignant melanoma cells on the smear had positive cytoplasmic staining.

Humoral antibody directed against the cytoplasm of malignant melanoma was traced in all the patients tested with malignant melanoma without metastases (54 primary or localized lesions); and in nine patients with halo naevus, three solitary and six multiple. The patients ages were: 8, 9, 12, 13, 13, 14, 17, 28, and 35 years. The small boy aged 9 years had had a solitary halo naevus on his cheek associated with a high titre of cytoplasmic antibodies. When his serum was retested six months after the lesion had been surgically removed no antibodies could be detected.

Cytoplasmic antibody to malignant melanoma cells was not found in patients with halo naevus (multiple lesions) that had resolved some years previously and had repigmented spontaneously; or in six with multiple melanocytic naevi (including two children with acutely erupting lesions and one man with scores of moles that had become acutely inflamed after dithranol treatment for his psoriasis); or in 46 with vitiligo (unassociated with halo naevi); or in four with "benign juvenile melanomas." Negative results were also found in 39 patients who had been referred with the diagnosis of malignant melanoma and who proved to have other conditions.

FIG 2. Positive cytoplasmic staining (patient's serum: F.I.T.C.-labelled IgG) of a malignant melanoma cell (smear preparation x 600).

We applied stringent criteria to detect circulating cytoplasmic antibody before recording a patient's serum as positive. All the