dilettante and will only discover something new by accident.

Your "single brilliant or lucky scientist" is my man from the start, provided that he will allow for the fact that years and years of conscientious painstaking endeavour are almost certain to result in a prejudiced approach. The whole history of the progress of mankind is witness to the fact that where a breakthrough has been made, it has come about through a combination of fortuitous circumstance and insight.

For this reason I cannot agree that to confirm researchers for life in a career structure would be an advance. In fact I believe that because "doctors and scientists undertake research during their progress to other posts" they are much more likely to have new ideas than those who enter research as a life-time occupation. There are plenty of these devoted workers who today can look back on 30 or 40 years of conscientious endeavour without having had a single new idea. This situation is inevitable if research is conducted by a vertical approach alone.—I am, etc.,

G. A. STANTON

Cambridge

¹ De Bono, Edward, *The Mechanism of Mind*, London, Jonathan Cape, 1969. *The Use of Lateral Thinking*, London, Jonathan Cape, 1967.

Tumbu Fly

SIR,—The fascinating accounts of dermal myiasis to tumbu fly (1 April, p. 58, and 15 April, p. 164) prompt me to report a further unexpected locus of the larvae. While working in East Africa a consultant surgeon produced a "worm" which he had removed by simple expression of a swollen healing appendectomy wound.

The patient was a young girl of 16 years, and both she and her surgeon were somewhat alarmed to find the parasite. Her wound healed without further difficulty. The larva was duly fixed in methanol, and a quick reference to Ashe and Spitz's excellent treatise on *Pathology in the Tropics*¹ made recognition simple.—I am, etc.,

RUTHVEN MITCHELL

Mount Vernon,
Lanark

¹ Ashe, J. E., and Spitz, S., *Pathology of Tropical Diseases*, Philadelphia, Saunders, 1945.

Urinary Candidiasis after Renal Transplantation

SIR,—We wish to report the use of the synthetic antimycotic agents 5-fluorocytosine and clotrimazole in the successful treatment of urinary candidiasis in a patient who had received a renal homograft.

A 32-year-old man received a renal homograft from his father. The graft functioned well although further operations were necessary to relieve ureteric obstruction. Gentamicin was then given to offset the effect of any bacteria introduced into the urinary tract by the passage of urethral and ureteric catheters, strains of *Klebsiella aerogenes* sensitive to gentamicin but resistant to ampicillin and carbenicillin having been repeatedly isolated from the perineal area before operation.

The urine, which was cultured daily, remained sterile until the 25th post-transplant day when *Candida albicans* was isolated. On the 30th day the urine contained more than 10⁵/ml. The organism was also isolated from

the mouth and throat although there were no clinical signs of infection. Because of its nephrotoxicity the use of amphotericin B was considered inadvisable. The patient was given 5-fluorocytosine 10 g daily in divided doses, reducing to 2 g on the third day, by which time the urine was sterile. On the sixth day, however, urine cultures were again strongly positive for *C. albicans*. Treatment was stopped for two days because of an operation to maintain urine drainage, but was recommenced with 2 g daily and continued for a further 10 days. Urine cultures for *C. albicans* remained strongly positive and the yeasts by now were shown to be resistant to 5-fluorocytosine. Three days later clotrimazole therapy, 100 mg/kg body weight was started. After five days urine cultures for *C. albicans* were negative. On the ninth and tenth days the patient was excessively drowsy and disorientated. Treatment with clotrimazole was stopped and his mental state rapidly improved.

There has been no recurrence of candiduria over the ensuing 10 months. The patient remains well and the graft is functioning satisfactorily.

The minimum inhibitory concentrations of the antimycotics for most of the candida isolates were measured. Serum and urine levels of 5-fluorocytosine and serum levels of clotrimazole were assayed. Yeast morphology agar (Difco), a cytosine-free medium, was used for all the sensitivity tests and assays. A sensitive strain of *Candida pseudotropicalis* was used for the assays of both drugs.

Mycological Findings During 5-Fluorocytosine Treatment

Day	<i>C. albicans</i> /ml	Levels (µg/ml)		
		Urine	Serum	Urine
0 ..	>10 ⁵ (0.25)*		0	0
2 ..	10 ⁵		5	100
4 ..	0		24	200
6 ..	10 ⁴ (≥1000)		28	200
9 ..	>10 ⁴ (≥1000)		1	60
11 ..	>10 ⁴ (≥1000)		5	100
17 ..	>10 ⁴ (≥1000)		6	150

*Mean Inhibitory Concentration for isolate in µg/ml.

The Table summarizes the mycological findings during treatment with 5-fluorocytosine. *Candida* initially isolated were sensitive to 0.25 µg/ml 5-fluorocytosine but were replaced by organisms resistant to more than 1,000 µg/ml. Serum levels varied from 1 to 28 µg/ml and urine levels from 60–200 µg/ml. The sensitivity of isolates was also determined by disc diffusion using discs containing 1 µg 5-fluorocytosine. Further examination of the initial isolate showed that it was not uniformly sensitive. Repeat disc sensitivity tests incubated at 37°C for 24 hours showed clear zones round the discs but when these were incubated at 30°C for the same time, colonies grew up to the discs. The minimum inhibitory concentration of clotrimazole for all the isolates tested was between 1 and 2 µg/ml. In the sera examined the levels never exceeded 0.6 µg/ml.

Liver function was assessed by measuring the serum levels of bilirubin, alkaline phosphatase alanine aminotransferase, and lactic dehydrogenase. During treatment with 5-fluorocytosine, there was a rise in the alkaline phosphatase level and isoenzyme studies showed that the increase was in the liver fraction. There was no disturbance of liver function during treatment with clotrimazole. Neither drug had an adverse effect on renal or bone marrow function.

Broad-spectrum antibiotics and immunosuppressive drugs are recognized factors in

the aetiology of severe candida infections.^{1,2} Both were given to this patient. Although gentamicin therapy had stopped before the candida was first isolated from the urine the antibiotic had probably selectively encouraged growth of the yeast. The failure of 5-fluorocytosine to eradicate the candida was disappointing. Strains of *C. albicans* resistant to clotrimazole have not been reported and attempts to induce resistance have failed.

Both these drugs are potentially useful in the treatment of systemic candida infections but are not free from toxic side effects. Disturbances of the bone marrow and liver function associated with 5-fluorocytosine have been reported previously.^{3,4} The disturbances were transient but in patients dying from the underlying disease toxic necrosis of the liver was demonstrated at necropsy by Record *et al.* (30 January 1971, p. 262).

The early trials have shown that as in this patient mild disturbances of the mental state may be associated with clotrimazole therapy. There are no reports of irreversible toxic effects associated with treatment with either drug.

We wish to thank Dr. J. Garrod, Roche Products Ltd. for supplies of 5-fluorocytosine, Mr. J. Dixon and Mr. C. S. Good, F.B.A. Pharmaceuticals Ltd., for supplies of clotrimazole, Miss M. McCready for the isoenzyme studies, and Dr. B. Moore for his encouragement and help.

—We are, etc.,

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Exeter

C. SHALDON
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Royal Devon and Exeter Hospital,
Exeter, Devon

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Research in Psychiatry

Sir,—Your leading article (8 April, p. 61) makes no mention of the contribution of general practitioners to this field. Yet their situation in the community can enable them to elicit both clinical and social data that are accurate and meaningful.

The article stresses the need for research "to be directed towards early ascertainment of the vulnerable." May I cite an instance of this? A pilot study to determine whether puerperal depression can be predicted from factors presenting in pregnancy has been devised and carried out by a consultant psychiatrist, three general practitioners, and a social worker. The findings, which were obtained from a series of 112 pregnancies and reported in the *Journal of the Royal College of General Practitioners*,¹ indicated four factors statistically significant by the χ^2 test:

- (1) Low tolerance to suffering at previous birth;
- (2) low tolerance to suffering associated with dysmenorrhoea;
- (3) husband away at time of birth; and
- (4) an ambivalent attitude towards, or an inability to accept, the pregnancy in the middle trimester.

About 100 general practitioners on the research register of the Royal College of General Practitioners have agreed to take part in a larger study, which it is hoped will confirm these findings. This investigation is about to start, and documents to record data are being distributed.

More participants will be welcome. May I, through these columns, ask interested general practitioners to write to me for further information.—I am, etc.,

H. R. PLAYFAIR

47 Wolseley Road, Plymouth PL2 3BJ

¹ Blair, R. A., Gilmore, J. S., Playfair, H. R., Tisdall, M. W., and O'Shea, C., *Journal of the Royal College of General Practitioners*, 1970, 19, 22.

Insulin and Oral Therapy in Diabetes

SIR,—We were interested in the paper by Drs. A. M. Tomkins and A. Bloom (11 March, p. 649). Our own experience at the Diabetic Clinic, Kingston, Jamaica, suggests that insulin therapy too may be needed less often than is generally realized.

One hundred consecutive diabetic patients (average duration of disease 2.7 years) were given an intensive course of re-education in the principles of dietary control. Obese patients (that is, those over 110% of ideal weight), who numbered 51, were usually put on an 800-calorie diet initially. Once proper carbohydrate restriction was practised (usually for the first time in the diabetic's life), only 7% of patients needed insulin for satisfactory control (as adjudged by a two-hour postprandial blood glucose of under 170 mg/100 ml and regular sugar-free urine tests). This compares with Dr. Bloom's figure of 26% among United Kingdom patients.¹

Of course, it may be that the patterns of diabetes in the United Kingdom and in Jamaica differ markedly. We would ask that a physician who sees an apparently insulin-dependent West Indian diabetic for the first time should bear in mind the possibility that the patient might be controlled without need for insulin. This is sometimes practicable even when the diabetic is young, thin, and initially ketotic.—We are, etc.,

G. S. HUMPHREYS

University of the West Indies
Kingston, Jamaica

D. G. DELVIN

Chislehurst, Kent

¹ Bloom, A., *Postgraduate Medical Journal*, 1969, 45 (Suppl. May, p. 5)

Care of the Mentally Handicapped

SIR,—Dr. A. Kushlick (11 March, p. 686) unfortunately appears to have misunderstood my letter (29 January, p. 308). Far from regarding improvements of living conditions and provisional facilities in hospitals as "unnecessary luxuries," I have attempted to draw attention to unacceptable living conditions for patients, and to inadequate facilities in hospitals. I have tried, however, to make the point that in comparing the quality of different forms of care no valid comparison is possible unless the cost of providing it is the same.

The purpose of my letter was to sound a warning note about the way this policy was being implemented, leaving aside the

fact that I consider that the Department of Health and Social Security has committed itself to the provision of community care on inadequate data. If the hospitals are going to be run down, and all improvement in the quality of services in hospitals stopped before adequate alternative provisions are made (which appears to be the case at present), then the hospitals will not be able to meet their commitments to the community they serve, and the present hospital population is going to be condemned to continue living under unacceptable conditions. However exciting and acceptable this prospect may be to people planning services at a distance, they cannot but fail to frustrate and dismay clinicians who will have the continuing duty of caring for their patients.—I am, etc.,

A. SHAPIRO

Harperbury Hospital,
St. Albans, Herts

Cyclophosphamide and Pigmentation

SIR,—Alopecia and acute haemorrhagic cystitis are well recognized side effects of cyclophosphamide, but we would like to draw attention to a case in which pigmentation occurred in the nails and teeth.

A 3-year-old boy was admitted on 11 April 1971 with a six-day history of generalized oedema. A diagnosis of the nephrotic syndrome was made. Initially he was treated with prednisone, but he became severely hypertensive with a blood pressure of 180/145 mm Hg and developed a spontaneous femoral artery occlusion in the left leg just above the knee, which was successfully treated with anticoagulants. Five days later he was started on a six-week course of methylodopa 125 mg t.d.s., and in order to cover the urgent need to reduce the steroids, cyclophosphamide was given in a dosage of 80 mg/day, starting on 1 May. This produced alopecia, and had to be discontinued after one month due to the development of acute haemorrhagic cystitis; but a satisfactory remission was induced.

On 10 May it was noticed that a brown discolouration had developed at the base of the finger and toe nails (Fig.), and there was a brown line on the teeth at the junction with the gums. The changes in the teeth have persisted but those in the nails have grown out.

We can find no reference to methylodopa causing such changes, though the tyrosine/dopa/melanin metabolic cycle might possibly be influenced thereby. Three cases of generalized skin pigmentation occurring during cyclophosphamide therapy have been reported independently by Glazebrook,¹ Rose,² Gibbs,³ Solidoro and Saenz,⁴ briefly mention skin and nail pigmentation as a side

effect of the drug, and one case of generalized pigmentation with darker pigmentation of the nails occurring during treatment of a case of Hodgkin's disease is known to the manufacturers, W. B. Pharmaceuticals Ltd.⁵ We can find no references to pigmentation of the teeth.

We wish to thank Professor N. R. Butler for permission to report this case.

—We are, etc.,

B. MARY HARRISON

C. B. S. WOOD

Department of Child Health,
Royal Hospital for Sick Children,
Bristol

¹ Glazebrook, G. A., in *Cyclophosphamide*, ed. G. H. Fairley and J. M. Simister, p. 128. Bristol, John Wright, 1964.

² Rose, F. C., in *Cyclophosphamide*, ed. G. H. Fairley and J. M. Simister, p. 120. Bristol, John Wright, 1964.

³ Gibbs, A. E., in *Cyclophosphamide*, ed. G. H. Fairley and J. M. Simister, p. 130. Bristol, John Wright, 1964.

⁴ Solidoro, A., and Saenz, R., *Cancer Chemotherapy*, 1966, 50, 265.

⁵ Simister, J. M., personal communication.

Pyramid Plan for Eye Care

SIR,—Professor J. G. Russell (18 March, p. 739) writes that authorities must strive to achieve the best results with the amount of national income allocated, and brings convincing evidence to show that team effort in a pyramid plan will increase cost-effectiveness and job-satisfaction in the dental service. The eye service has much in common with the dental service. It has a community-based sector (general ophthalmic service) and a school sector; the ratio of community attendances to outpatient attendances to inpatients in dentistry is 370:38:1, in ophthalmology 56:24:1; (in general surgery the ratio is —:3.5:1); it requires expertise and instruments not available in the general medical service; and it is heavily involved in technical procedures which can be carried out by non-medical staff. In the eye service the unique conceptual skills of the ophthalmologist and the technical skills of the ophthalmic optician are squandered,

cost-effectiveness is low, and job-satisfaction is low. There is room for improvement.

In 1944 Squadron Leader Scoular wrote¹ that it was opportune to try to improve the eye service of the nation and suggested that eye clinics should be set up staffed by ophthalmologists and opticians. These clinics would provide sight tests, diagnosis and treatment of disease, and dispensing of glasses and only those requiring operations or special treatment would be sent to hospital. In 1947 the Eye Service Committee in its report² stated "We feel sure that in a service in which ophthalmologists and opticians work together as a team mutually satisfactory arrangements can and will be