lack of decent part-time job opportunities and training posts in most hospitals, there is another glaring inadequacy for both doctors and other women who work in the National Health Service: that is, lack of hospital crèches and nurseries.

I have recently contacted a large number of hospitals in the London area to find out just what is the current situation. Within the teaching hospitals, only one, namely, Charing Cross (Fulham branch), had a crèche, and in many of the others, even where rebuilding is planned or in operation, only one had plans for a crèche within the next few years. In most there was no crèche planned at all and in another it would be at least 10 to 15 years before one was planned.

Perhaps the worst aspect of the situation is that new hospitals are being planned and built without any facilities for crèches. What do those who are responsible for this situation expect women doctors, nurses, and other women in the health service who are starting a family to do during the preschool years?—I am, etc.,

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Vitamin B₁₂ and Folate Metabolism

SIR,—Your series on the scientific basis of clinical practice is excellent, but there is a misinterpretation in the article on vitamin B₁₂ and folate metabolism (26 February, p. 556). In the section on transport it is stated that transcobalamin II is a weak binder and the vitamin B₁₂ attached to it is readily released for urinary excretion. The fact that B₁₂ bound to this protein, more often referred to as transcobalamin II or TC II, is removed rapidly from plasma does not mean that the binding is weak but that the complex is taken up by tissues. A recent review of my own¹ gives what is generally considered to be the function of TC II. When studied in vitro, the bond between TC II and B₁₂ is strong. Some of the binding properties are given in a series of articles from the laboratory of Dr. Lous, Copenhagen.² I know of no evidence that B₁₂ bound to TC II is readily excreted into the urine, but there is substantial evidence to the contrary.

Although perhaps unintentionally, the review gives the impression that TC II does not play a large role in the transport of vitamin B₁₂. Hakami *et al.*³ have recently described the serious consequences of congenital absence of TC II. The loss of this transport protein alone causes a severe megaloblastic anemia.—I am, etc.,

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- Hall, C. A., *British Journal of Haematology*, 1969, **16**, 429.
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Total Replacement of the Hip

SIR,—Your leading article on total hip replacement (22 April, p. 177) quite rightly stresses the excellence of the vast majority of results after this type of surgery whatever technique is used, but the failures which

occur, particularly when acrylic cement is used, merit more detailed consideration.

Bone cement carries with it a small but definite risk of a fatal episode at the time of intervention, much higher in patients with femoral neck fractures than those with osteoarthritis coming to reconstructive surgery, for reasons which are still not quite clear. This risk, which is a small one, would be fully justified if no satisfactory alternative were available, but our experience with the uncemented metal on metal replacement has shown that these joints can give a satisfactory solution to the problem of the arthritic hip joint, provided attention is given to the mechanics of the articulation and a reasonable technical standard of implantation is employed.

You quote from Charnley.¹ He reports a mortality of 2.1% and a risk of deep seated infection, leading eventually to a pseudarthrosis, of 3.5%. This gives a total failure rate of almost 6%, a figure which is certainly far above that in an uncemented articulation. Our mortality in over 900 total hip replacements was 1%, and the rate of deep seated infection, occurring both early or late, was a further 1%, giving a total failure rate of 2%. Although in some of the earlier replacements both loosening and mechanical failure were an occasional problem, our current revision rate for these two complications is little more than 1%. It is important to remember that whereas loosening in an uncemented articulation may present as no more than a radiological curiosity, in those replacements which rely on the use of cement loosening is almost invariably painful.

You are right to insist that the standards of asepsis in any theatre undertaking this type of work must be high, and it may well be that Charnley's enclosure will be shown to have reduced the infection rate at Wrightington and come into common use elsewhere. For many years, however, most of us will have to work under different conditions, and it would be wrong to assume that this type of surgery cannot be undertaken safely in an ordinary orthopaedic unit.

Most patients after a total hip replacement return to a functional level which is appropriate for their age, their joints are painless, and they have a reasonable range of movement. We have, however, passed the stage of appraising the excellence of the results of this operation, and must look very seriously at the risks which are inherent in each of the methods of total hip replacement, and must evaluate to what extent they are due to the environment in which the operation is performed and how far they are related to the materials which are used and the way in which the joint is embedded.—I am, etc.,

P. A. RING

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- Charnley, J., *Journal of Bone and Joint Surgery*, 1972, **54B**, 61.

Donors for Organ Grafting

SIR,—I am sorry the letter by Dr. H. Hillman and Mr. T. M. Aldridge (1 April, p. 48) seems to have attracted no comment. It is important to avoid popularizing terms in a manner which is not in keeping with their essential meaning. "Irreversible brain damage" (which is proposed as a legally certifiable condition permitting withdrawal of intensive care and organ removal) must

surely occur in varying degrees; and very likely much brain "damage" (if that implies cell or fibre destruction) is largely irreversible. Doubtless this term can properly be applied to many cerebral lesions, both large and small, in old and young (where it is commonly used); and it includes conditions of major and minor importance as regards survival—for example, strokes, head injuries, and even perhaps the normal processes of ageing.

This is clearly not what is intended by those proposing this term for intensive care or transplant purposes (otherwise there could be no shortage of donors), and it would seem advisable to choose a more suitable term. Some qualification such as "gross irreversible brain damage" would help clarify the position, but "damage" may be unduly vague (with many milder clinical usages). Other possibilities such as "gross brain destruction" or "gross cerebral necrosis" also merit consideration; they may seem too precise and extreme, but this is what the clinical situation requires.—I am, etc.,

ELMAN POOLE

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Career Structure for Cancer Research

SIR,—I feel that there are certain points in your leading article (8 April, p. 63) on this subject which require elucidation. For example, you use the term "first-class brain" in a context which appears to imply that we all know what this is and the problem is to evolve a career structure which will make it worthwhile for these people to enter the research field. There are, however, good reasons for supposing that an examination how the brain works in solving problems would result in a more fruitful and less expensive effort in this field.

De Bono¹ has shown that thinking processes devoted to the solution of problems can be either vertical or lateral. Vertical thinkers are those who believe that problems can be solved by a conscientious and painstaking progress from one most likely choice to the next and so on, deeper and deeper into an expertly dug hole. "To use his own analogy—as you say, a 'deeper understanding of living processes.'" Lateral thinkers deliberately choose an improbable pathway, "moving sideways," rejecting approaches that do not square with the facts, and refusing to get so deeply involved in any hole as to get out of touch with the rest of the field.

A serendipitist is one who is skilful in arriving at fortunate chance discoveries. This apparent paradox is resolved by the lateral thinker, who deliberately uses chance as a means of finding a solution. His success depends on years of preparation by a vertical approach during which he builds up a mass of information preparatory to his lateral skirmishes into the unknown. The first-class brain therefore will be a combination of sustained academic endeavour but which will retain a freshness of outlook. The researcher who is just expert but pompous will get ever deeper into his interminable hole, developing a jargon that only he and his immediate associates can understand and which is not reducible to simple terms. The lateral thinker with no background of conscientious study in depth will become a

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

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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

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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 ⁸ (0.25)*		0	0
2 ..	10 ⁸		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. McCreedy for the isoenzyme studies, and Dr. B. Moore for his encouragement and help.

—We are, etc.,

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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.