to discuss depression and the causes of his sadness, and may even begin to talk about the relationship of his overactivity to his hopes of avoiding its becoming apparent to himself or others. When this is so, the attempt to help the child to grieve normally may not be very different from what is done frequently with adults with greater or less success.—I am, etc.,

W. CLIFFORD M. SCOTT

Montreal, Quebec

Calcitonin in Osteogenesis Imperfecta

SIR,—Your recent leading article (17 February, p. 371) refers to a preliminary investigation on the effect of calcitonin in osteogenesis imperfecta. Several workers have used calcitonin in this disorder[1 2] and have suggested[1] that it may have a therapeutic place. We think that this suggestion is premature. Ignorance of the cause of a disorder need not necessarily prevent attempts at treatment. Thus in Paget's disease, where the cause remains completely obscure, there is overwhelming biochemical and histological evidence of increased and disorderly bone formation and resorption, which is presumably the direct cause of the changes in the bones and the complications which follow. Attempts to suppress this increased bone turnover therefore seem logical, and in Paget's disease the well-documented ability of calcitonin to reduce bone resorption is therapeutically useful.

In osteogenesis imperfecta the situation is different. Some measurements of bone histology[3] and urinary total hydroxyproline excretion[4] suggest excess bone resorption, although these findings are not unanimously accepted. Even if resorption is increased it is by no means clear that it is an important part of the disease process and should therefore be suppressed, rather than a physiological response to other primary changes in the bone. In either case calcitonin will reduce total hydroxyproline excretion, but there is no evidence that this effect is desirable therapeutically.

There is no consensus of opinion about the cause of osteogenesis imperfecta. Recent work on abnormal pyrophosphate[5] and leucocyte metabolism has not been confirmed,[6 7] and there is no convincing evidence of a primary defect in mineralization. On clinical and pathological grounds it has been thought for many years that the inherited features of the disease are due to an abnormality of collagen. Knowledge of collagen biochemistry is now sufficiently advanced[8] for such a suggestion to be directly investigated in tissues or in fibroblasts grown from them. Preliminary data suggest an abnormality of collagen cross-linking in at least some patients with osteogenesis imperfecta[9] and agree with the clinical observations that it is not a homogeneous disorder. Recent work, which shows that the types of cross-link in fetal collagen differ from those of later life,[10] and that there are chemical differences between the collagen of cartilage and bone,[11] provides for the possibility of many collagen defects which could resemble each other clinically.

Osteogenesis imperfecta is a significant cause of severe crippling, and any advance in treatment is to be welcomed. At present, however, there seems to be insufficient evidence to suggest that calcitonin is a rational treatment for this disorder. Since calcitonin is commercially available there is a risk that it may be widely used in this disease before the proper clinical trials have been carried out.—We are, etc.,

R. SMITH
M. J. O. FRANCIS
R. G. G. RUSSELL

Nuffield Orthopaedic Centre,
Oxford

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Sympathomimetic Amines and Antidepressant Agents

SIR,—The experimental evidence presented by me and my colleagues (10 February, p. 311) that imipramine potentiates the pressor effects of sympathomimetic amines is imaginatively discounted by Dr. G. G. Wallis (3 March, p. 549), who pictures our results as being due to experienced clinical pharmacologists frightened by their own knowledge as well as designing their experiments unusually badly. We do not recognize the scene he paints and indeed took special precautions to avoid subjective influences.

Dr. Wallis assumes that imipramine always preceded the monoamine oxidase inhibitor. This was not so. Orders of administration of antidepressants were randomized, as were orders of intravenous infusions (as mentioned in the paper), and subjects did not know when doses and drugs were changed. We regret that failure to report the order of experiments led Dr. Wallis to an erroneous supposition.

Further, a rise in blood pressure precipitated by anxiety would ordinarily be accompanied by a rise in heart rate. We found, however, that the pressor response during phenylephrine and noradrenaline infusions was always accompanied by marked bradycardia. The control infusions gave reproducible responses in this series of experiments as in the many previous series we have conducted.

Our results accord with those of others in both man[1] and animals.[2] There is now substantial evidence that sympathomimetic amines can produce serious cardiovascular effects in patients being treated with tricyclic antidepressant agents.[3] We think it important that clinicians should be aware of this.—I am, etc.,

A. J. BOAKES

Charing Cross Hospital,
London W.6

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Actinomycin D for Wilms's Tumour

SIR,—Dr. H. W. C. Ward's letter (17 February, p. 420) about the advisability of the use of actinomycin D for Wilms's tumour is of interest because it shows how easy it is to arrive at the wrong conclusions. The results for Wilms's tumours in the Birmingham region are indeed rather bad. Dr. Ward states that between 1965 and 1969 only six out of 29 children treated with actinomycin D survived, a survival rate of just over 20%, while of those patints who did not receive actinomycin D seven out of 17, or about 40%, survived. The latter figure corresponds roughly to the survival rates which were obtained in the main paediatric surgical centres before 1958. For instance, we in Liverpool operated on 21 children with Wilms's tumour between 1949 and 1958 with nine (42%) survivors.

It is true that a course of actinomycin D by itself will not greatly improve the survival rate, which depends to a large extent on a much more radical type of surgery for this condition than used to be practised, on repeated courses with cytotoxic drugs, and on a much more aggressive treatment of metastases. If this is done the survival rate improves greatly, as has been shown by many American authors. Our experience in Liverpool has been similar to theirs, and of 21 patients with Wilms's tumours operated on between 1 January 1966 and the middle of 1971 17 (81%) are still alive. The staging of these children shows a very similar distribution to those in Birmingham: stage I, 8/8; stage II, 4/6; stage III, 3/4; stage IV, 3/3.

Rather than to attempt to draw conclusions from the different survival rates of two bad series one should pose the question why so few children with Wilms's tumours survived in Birmingham compared with neighbouring regions, and in this connexion it is perhaps not incidental that during the period mentioned by Dr. Ward no paediatric surgeon practised in Birmingham. It will be interesting to see whether the results will improve since the appointment of a paediatric surgeon to the region.—I am, etc.,

P. P. RICKHAM

University Children's Hospital,
Zurich, Switzerland

Latent Morbidity after Abortion

SIR,—Let us set the record straight about latent morbidity after termination of pregnancy. Wynn and Wynn,[1] cited in your leading article (3 March, p. 506), repeatedly refer to an increase of 50% in perinatal mortality after "abortion," quoting the 1958 British Perinatal Mortality Survey.[2] Do they not appreciate that termination of pregnancy was very unusual in British hospitals in March 1958, that the term "abortion" was used to define all previous and mainly spontaneous abortions, and that previous ectopic pregnancies are considered in the same table:

No. of abortions or ectopics:	0	1	2	3	4+
Survey mortality ratio	94	131	186	170	390
Perinatal mortality (%)	3·3	4·4	7·0	5·6	13

Previous premature birth produced very similar effects: