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.,

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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 suggested¹ 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 histology³ and urinary total hydroxyproline excretion⁴ 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 pyrophosphate⁵ 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 advanced⁸ 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 imperfecta⁹ 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.,

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- 1 Castells, S., Inamdar, S., Baker, R. K., and Wallach, S., *Journal of Pediatrics*, 1972, **80**, 757.
- 2 Caniggia, A., and Gennari, C., *Calcified Tissue Research*, 1972, **9**, 243.
- 3 Robichon, J., and Germain, J. P., *Canadian Medical Association Journal*, 1968, **99**, 975.
- 4 Langness, U., and Behnke, H., *Metabolism*, 1971, **20**, 456.
- 5 Solomons, C. C., and Styner, J., *Calcified Tissue Research*, 1969, **3**, 318.
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- 7 Russell, R. G. G., Bisaz, S., Donath, A., Morgan, D. B., and Fleisch, H., *Journal of Clinical Investigation*, 1971, **50**, 961.
- 8 Grant, M. E., and Prockop, D. J., *New England Journal of Medicine*, 1972, **286**, 194.
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- 10 Bailey, A. J., and Robins, S. P., *Febs Letters*, 1972, **21**, 330.
- 11 Miller, E. J., *Biochemistry*, 1971, **10**, 1652.

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 man¹ 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.,

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- 1 Svedmyr, N., *Life Sciences*, 1968, **7**, 77.
- 2 Goldman, V., Astrom, A., and Evers, H., in *Proceedings of the Third Asian and Australasian Congress on Anaesthesiology*, ed. L. Shea and B. Dwyer, p. 517. Sydney, Butterworths, 1970.
- 3 Boakes, A. J., Laurence, D. R., Lovel, K. W., O'Neil, R., and Verrill, P. J., *British Dental Journal*, 1972, **133**, 137.

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 patients 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.,

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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:

No. of premature births:	0	1	2	3	4+
Survey mortality ratio	84	152	186	230	452
Perinatal mortality (%)	2.6	5.0	7.0	7.7	14.9

Termination of pregnancy is likely to have less effect than this on future perinatal mortality.

In your leading article you quote a 40% increase in prematurity following termination of pregnancy. This is the correct figure after one such abortion, but Wynn and Wynn¹ and Gordon³ quote from Hungarian reports showing an increase of more than 100% after three or more terminations in 1968:

No. of terminations	0	1	2	3+
Prematurity rate (%)	9.3	13.0	16.6	20.6

The prematurity rate does not normally increase with parity by more than 2% as the figures from the 1958 British survey show:

Parity	0	1	2	3	4+
Prematurity rate (%)	7.6	5.4	6.7	7.0	7.4

Assuming that the increase in prematurity rate after termination in Britain will be similar to that in Hungary, a rise of about 6% is to be expected. As the perinatal mortality in all prematures is about 26.4% the increase in perinatal mortality after termination will be about 1.6% (16 per 1,000 births).

I predict that the contribution of the increased prematurity rate after termination will affect perinatal mortality in Britain as follows:

No. of terminations	0	1	2	3	4+
Perinatal mortality (%)	2.5	3.0	4.1	5.0	6.0

In Hungary the perinatal rate has doubled since the introduction of abortion on request.⁴ These findings seems likely to be accounted for by the increased prematurity rate and limited special care facilities which are at present available there for neonates. Any increased incidence of placental insufficiency after termination of pregnancy is at best not proven, and we must continue to look for other factors contributing to increased perinatal mortality.

Whatever the answers, the conclusion must be that if we accept liberal abortion in the young, perinatal mortality in Britain can only increase dramatically in this decade.—I am, etc.,

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¹ Wynn, M., and Wynn, A., *Some Consequences of Induced Abortion to Children Born Subsequently*, London, Foundation for Education and Research in Childbearing, 1972.

² Butler, N. R., and Bonham, D. G., *Perinatal Mortality*, London, Livingstone, 1963.

³ Gordon, H., *British Journal of Hospital Medicine*, 1973, 9, 303.

⁴ Jurukovski, J., and Sukarov, L., *International Journal of Gynaecology and Obstetrics*, 1971, 9, 111.

Mode of Action of Verapamil

SIR,—We thank Dr. D. G. McDevitt and R. G. Shanks (17 March, p. 681) for their comment on our report on the comparative effectiveness of verapamil and propranolol in the treatment of angina pectoris. We certainly did not claim that verapamil blocked β -adrenoceptors. In fact, we were careful to state that our experience suggested that in man an important action of verapamil was to augment the effect of vagal tone on the specialized conducting tissue of the heart. This statement neither ignores nor contradicts the published information about the effect of verapamil in man. Published evidence over recent years has conclusively shown that the mode of action of verapamil consists in the inhibition of influx of calcium ions into the myofibril with a resultant reduction in activity of myofibrillar adenosine triphosphatase and a reduction in oxygen consumption and energy output on the part of the cell.¹

Fitzgerald,² at the Seventh Pfizer International Symposium held in Edinburgh last May, stated that one of the modes of action of beta-blocking agents was to unmask the effects of physiological vagal tone. Though verapamil is not a beta-blocking agent, because of its vagomimetic direct action in the specialized conducting tissue of the heart, it might be expected to be of value in the treatment of tachycardiac angina induced by effort. The end-result of either blocking the sympathetic nervous system or augmenting the effects of the vagus on the heart would be expected to be very similar. Our opinion remains unaltered—namely, that "Our results indicate that both propranolol (100 mg three times a day) and verapamil (120 mg three times daily) significantly reduce the heart rate at rest and throughout the exercise test, and this action together with hypotensive effects may account for the value of these preparations in the treatment of exercise-induced angina pectoris."—We are, etc.,

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¹ Fleckenstein, A., *Arzneimittel-Forschung*, 1970, 20, 1317.

² Fitzgerald, J. D., in *Effect of Acute Ischaemia on Myocardial Function*, ed. M. F. Oliver, D. G. Julian, and K. W. Donald. London, Churchill Livingstone, 1972.

Road Accident Prevention

SIR,—I am much interested in Dr. Elizabeth Vaughan's letter (31 March, p. 803) in which she asks for the founding of a medical body concerned with the epidemiology of accidents. It is probably a reflection on our publicity that she does not know of the existence of the Medical Commission on Accident Prevention.

This was set up in 1964 by the Royal Colleges of Surgeons, Physicians, Gynaecologists, and General Practitioners and other academic bodies, with the considerable support of the B.M.A. Research is conducted on problems relating to accidents in the four environments of transport, the home, industry, and recreation. Conferences are held on these matters as well as upon the problems of rescue and resuscitation at the sites of accidents, and we are particularly interested and involved in the recent develop-

ment of road rescue schemes being organized throughout the country by general practitioners. Our medical expertise is readily available with advice whenever it may be sought.

Dr. Vaughan should know that we have published valuable and influential reports, including "Medical Aspects of Fitness to Drive" and "Medical Aspects of Home Hazards." We are sending copies of these reports to Dr. Vaughan, but the medical profession as a whole should know of our existence. Greater attention to the medical factors, both physical and psychological, is vital in any campaign in this field.—I am, etc.,

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Contact Sensitivity to Toothpaste

SIR,—We read with interest the report by Dr. L. G. Millard (17 March, p. 676) of three cases of contact dermatitis due to cinnamon in a recently marketed toothpaste. We have been investigating a small group of 10 patients with symptoms such as those described by Dr. Millard. Only three had been referred to the clinic because of their symptoms and in no case had sensitivity to toothpaste been considered as the cause. It was, indeed, the patients' own observation that led to an inquiry into this possibility and subsequent patch testing to the full range of ingredients of the preparation. Patch tests were strongly positive to 1% cinnamic aldehyde.

As the patients had developed symptoms soon after the toothpaste was marketed, we questioned the next 600 patients attending the clinic about their use of toothpaste and any adverse reactions they might have experienced. Two other cases of apparent sensitivity of a similar type came to light and these were tested with the same result. We were not able to establish any link between the use of this toothpaste and conditions such as hand eczema and chronic urticaria.

We proceeded to circulate all dental and general practitioners in our areas asking for any patients with symptoms of this type to be referred. The exercise produced, among a plethora of oral pathology, two further cases. Several other patients complained of similar symptoms but had not used this particular brand of toothpaste and had negative test results to cinnamic aldehyde and related chemicals.

Certain features are of particular interest. Most patients with adverse reactions developed these symptoms soon after the toothpaste was marketed, a phenomenon well known in the cosmetic and toiletry field. One patient with positive patch-test reactions was able to continue using the toothpaste without ill effect, though the others, naturally, have changed the brand. Though sensitization of the skin to cinnamon is well recognized, mucosal reactions have rarely been reported and the mucosal epithelium has always been regarded as less rapidly sensitized. It is obviously easy to overlook toothpaste and mouth washes as a cause of stomatitis and cheilitis, and Dr. Millard is to be congratulated on his speedy recognition of the relationship in his cases. His report has drawn attention to an area of contact der-