Anaesthetic Contamination

SIR,—Your leading article (24 March, p. 693) draws attention to the statistical evidence suggesting an association between various toxic effects and pollution of the atmosphere with volatile anaesthetics in operating theatres and recovery areas. However, for those not fully familiar with this subject a number of points require clarification.

The implication that the problem is primarily related to halothane may be misleading. Nitrous oxide should receive equal attention. Anaesthesia with halothane is almost always accompanied by nitrous oxide and in addition most "non-halothane anaesthetics" will have nitrous oxide as a constituent. Nitrous oxide is thus probably the most commonly administered anaesthetic in use today. It is present in the atmosphere of operating areas and has been detected in the expired air of personnel working in these areas. In animals nitrous oxide is teratogenic, as are all the volatile anaesthetics, at anaesthetic concentrations, and circumstances have been suggested under which nitrous oxide could be carcinogenic¹. Furthermore, the original report² drawing attention to teratogenic effects in theatre personnel was made in operating theatres where nitrous oxide and ether were the atmospheric contaminations; halothane was not in use. As nitrous oxide does not appear to be adsorbed by activated charcoal, Dr. R. S. Vaughan and his colleagues (24 March, p. 727) may be able to carry out an interesting clinical trial by using their Cardiff Aldasorber to remove halothane from the atmosphere.

With regard to halothane, although the original work by Cascorbi *et al.*⁴ did suggest that halothane stimulated its own metabolism, their more recent study⁵ shows a wide scatter in both anaesthetists and non-anaesthetists; the evidence that halothane influences its own metabolism is not convincing. Even so, at present all available evidence shows that neither normal nor "abnormal" metabolism results in the formation of hepatotoxic metabolites, either in man or in many animal species.⁶ Furthermore, the 20-year survey of causes of death in American anaesthetists⁷ to which you refer did not demonstrate an increased incidence of liver disease as compared with the general population. As to removing the risk of anaesthetic contamination, your statement that this "depends in the first place on the provision of large operating and recovery rooms with air conditioning that changes the air several times an hour" is not consistent with the fact that most of the surveys on pollution have been carried out in well-ventilated, air-conditioned operating areas in North America.

Since reduction of atmospheric pollution in operating areas is not straightforward, it is essential to establish that a problem exists in relation to toxic effects on personnel, particularly as the most obvious available method of reducing pollution (avoidance of inhalational anaesthetics) may be detrimental to patients undergoing general anaesthesia.—I am, etc.,

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- ⁴ Cascorbi, H. F., Blake, D. A., and Helrich, M., *Anesthesiology*, 1970, 32, 119.
- ⁵ Cascorbi, H. F., Blake, D. A., and Helrich, M., in *Cellular Biology and Toxicity of Anaesthetics*, ed. B. R. Fink p. 197. Baltimore, Williams & Wilkins, 1972.
- ⁶ Strunin, L., and Simpson, B. R., *British Journal of Anaesthesia*, 1972, 44, 919.
- ⁷ Bruce, D. L., Eide, K. A., Linde, H. W., and Eckenhoff, J. E., *Anesthesiology*, 1968 29, 565.

Serum Alkaline Phosphatase and Rickets

SIR,—The recent report by Dr. W. T. Cooke and others (10 February, p. 324) requires comment since its provocative conclusions are not supported by the results presented.

Firstly, the authors chose to study an age range for each sex (14-17 years) during which the rapid changes in serum alkaline phosphatase level associated with puberty are at their peak in boys while almost complete in girls,¹ who mature two years earlier.² It would therefore have been more logical to screen girls of 12-15 and boys of 14-17 if their aim was to detect "biochemical rickets" during puberty. Even then, yearly age corrections within each group would be important.

Secondly, their supposed normal range of alkaline phosphatase levels for the three-year period, 8-17 K.A. units in girls and 9-23 K.A. units in boys, appears to be stated without supporting evidence and in apparent contradiction to the data they present. Despite their analytical method for alkaline phosphatase, which gives results at least 19% higher than those of other workers, they still adopt an arbitrary upper limit of 30 K.A. units and state that the majority of children with values above this limit probably have rickets. The simple calculation which follows from this is that the majority of a proportion approaching 41% of all schoolchildren in the age group studied (14-17 years) have the disease. This conclusion, certainly with regard to schoolchildren of Caucasian ancestry, is perhaps more likely to be based on the false premises with which they started. In order to have some value, any screening test must at least reveal some proportion of clinical disease among its positive readings. Fig. 2 of the report (the legend to which is, incidentally, faulty) suggests that about 40% of Caucasian boys had serum alkaline phosphatase levels above 30 K.A. units; the fact that none of these children had radiological evidence of rickets surely raises questions about the reliability of the authors' definition and about the whole interpretation of their results.

It may not be valid for them to assume that values in healthy children have a normal gaussian distribution, since the data of one of us (J.M.R.) indicate a log-normal distribution of alkaline phosphatase levels above the age of 11. Allowing for the 19% higher phosphatase values obtained by their laboratory method, their actual mean levels over the limited age range studied (very much higher than the supposed normal range which they quote) agree reasonably closely with the results obtained by one of us in a study of London schoolchildren of Caucasian ancestry.¹

They stress the importance of low urinary calcium and high hydroxyproline excretion in their diagnostic procedure, while their own results (figs. 3 and 4) emphasize the

complete lack of correlation between these measurements and radiological evidence of rickets.

Finally, the report lays great store by the effect of a large daily dose (1.25 mg) of calciferol in lowering the highest phosphatase values found among healthy children. The effects of vast doses of calciferol during the normal puberty growth spurt have not been previously studied; however, it may be just as valid to draw the exactly opposite conclusion from the data presented. The authors' fig. 5 shows that healthy boys maintained alkaline phosphatase levels in the region of 40 K.A. units during the whole period from 1 to 6 months following an entirely unphysiological dose of calciferol (125 times the usually recommended antirachitic dose of 400 IU/day). On the authors' criteria, most of these children would therefore still have rickets. Thus the "rickets" from which these children are supposed to be suffering could not even be cured by its specific therapy given in overdosage.

The problem of rickets and osteomalacia among our immigrant Asian community has been recently stressed and need not be underestimated. A proper understanding and solution of these problems may not be helped by confusing them with physiological changes at puberty which the present report does nothing to distinguish.—We are, etc.,

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¹ Round, J. M., *British Medical Journal*, 1972, 3, 114.

² Tanner, J. M., *Growth at Adolescence*, 2nd edn. Oxford, Blackwell, 1962.

Hyperactive Children

SIR,—It is surprising indeed that today, when in adults the various forms of depression and defences against depression are continually before the general practitioner, there is no mention in your leading article (10 February, p. 305) to the relationship of depression and mania in children to hyperactivity. It was many years ago that the late D. W. Winnicott, the paediatric psychoanalyst who added so much to our understanding of ways of making contact with children, discussed the frequency of manic or hypomanic activity as a defence against depression in children.

The constant, restless, seemingly purposeless activity, the impulsiveness, the reduced attention span, the distractibility, the inconsistency, the emotional immaturity and irritability, and the poor judgement which you describe as part of the picture of the hyperactive child are part of the picture of mania at any age. Unrecognized sleeplessness is often present as well. These symptoms may be due to many causes; surely by now we should all be alert to the possibility that one of these causes is a defence against depression. The presence of more or less conscious wondering whether one should give in to depression or "fight it off" by over-activity and cheerfulness is not confined to adults.

When manic excitement is considered as a possibility, then in interviewing the child one is much more apt to take a history which will include the possibility of the child being chronically depressed. In the simplest examples the child may be surprisingly ready

¹ Johnson, E. B., *Lancet*, 1972, 2, 824.

² Vaisman, A. I., *Ekspierimental'naia Khirurgiya i Anestziologiya*, 1967, 12, no. 3, 44.

³ Vaughan, R. S., Mapleson, W. W., and Mushin, W. W., *British Medical Journal*, 1973, 1, 727.

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.
- 6 Baehner, R. L., *Journal of Pediatrics*, 1972, **80**, 346.
- 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.
- 9 Francis, M. J. O., Smith, R., and Macmillan, D. C., *Clinical Science*. In press.
- 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: