Against this background the experience of Guy's Hospital following excision of the proximal row, now supported by Mr. J. S. Batchelor (December 8, p. 1540), is of interest. Yet I wonder what percentage of patients did in fact return to hard manual work after this operation.—I am, etc.,

Birmingham Accident Hospital,
Birmingham 15.

WILLIAM GISSANE.

Effects of Tetracycline

SIR,—It has come to my attention that several communications dealing with tetracycline have recently appeared in this journal. Since some of the authors of the remarks transmitted to the journal are apparently unaware of the results of several recent investigations which bear on this topic, I would like to indicate briefly what these studies have shown.

In our original publication¹ we described inhibition of growth and the development of the malformed, incompletely mineralized bones in the chick embryo when injected with a single dose of 2.5 mg. of tetracycline. At this time we remarked that "inasmuch as tetracyclines are frequently employed in clinical practice, the results we have reported may be important."

Subsequent studies have amplified the above findings considerably. The eggs of laying hens² fed trace amounts of tetracycline in their ration, when subsequently hatched, exhibited tetracycline in the bones of 2-week-old chicks.

Pregnant rats³ injected with the drug during various intervals of the pregnancy cycle resulted in the production of embryos very much reduced in size and weight. These experiments also demonstrated that 10–12 days was the most critical period for the production of growth inhibition observed.

Studies on the human infant⁴ have shown uptake and retention of transplacentally acquired tetracycline in bones and teeth. In addition, studies on the newborn infant have shown that oral administration of 100 mg./kg. of tetracycline for 10 days resulted in a decrease in the linear growth of the fibula amounting to 40% when compared with the normal rate. After cessation of drug therapy the growth rate for the subsequent observation period (10 days) returned to normal.

We have demonstrated⁵ uptake and retention of tetracycline corresponding to zones of demineralization in the teeth of rats injected with the drug on successive days. A recent study⁶ of the teeth of 50 children at the age of 1 year, all of whom had been treated with tetracycline in very early childhood, showed the following: (1) A very high incidence of pigmentation, (2) enamel hypoplasia, pitting of enamel, and malformed cusps. Also, the pigmented teeth were observed to be highly caries-susceptible. In our own clinic⁷ two children 5 and 7 years of age having a history of tetracycline therapy in early childhood exhibit tetracycline pigmentation of the teeth and rampant caries.

In summary, administration of tetracycline to laboratory animals at appropriate levels and time development results in inhibition of growth, retention of the drug, and hypomineralization of skeletal structures. In the human infant, studies have shown incorporation and retention of the drug and also inhibition of linear growth of bones in the post-natal period. Children to whom tetracycline was administered in early childhood exhibit tetracycline pigmentation in the enamel and dentin, enamel hypoplasia, malformed cusps, and in some instances rampant caries.

We believe that ample evidence has been presented above to warrant caution in the use of this drug during pregnancy and early childhood.—I am, etc.,

University of Texas,
Dental Branch,
Houston 25, Texas, U.S.A.

GERRIT BEVELANDER.

REFERENCES

- ¹ Bevelander, G., Nakahara, H., and Rolle, G. K., *Nature (Lond.)*, 1959, **184**, 728.
- ² Rolle, G. K., Bevelander, G., and Fisher, H., *Amer. J. vet. Res.*, 1962, **23**, 315.
- ³ Bevelander, G., and Cohlman, S. Q., *Biologica Neonatorum*, in press.
- ⁴ Cohlman, S. Q., Bevelander, G., and Bross, S., *Antimicrobial Agents and Chemotherapy*, 1961, p. 340.
- ⁵ Bevelander, G., Rolle, G. K., and Cohlman, S. Q., *J. dent. Res.*, 1961, **40**, 1020.
- ⁶ Wallman, I. S., and Hilton, H. B., *Lancet*, 1962, **1**, 827.
- ⁷ Lunin, M., personal communication, 1962.

Thiotepa and Breast Cancer

SIR,—I would like to congratulate Drs. A. Lyons and G. Edlstein on their reasoned report on the place of thiotepa in breast-cancer treatment (November 17, p. 1280). I would appreciate the opportunity to comment on two of their observations which appear to me to be of especial importance.

(1) Among their conclusions they state, "The fact that hypophysectomy and thiotepa were effective in similar types of disease suggested an endocrine basis for its action." Their Table II shows a relatively greater sensitivity of premenopausal cases to thiotepa in that five of eight premenopausal cases responded but only 12 of 32 postmenopausal cases ($p < 0.2$). The high level of thiotepa dosage used (180–300 mg. in two to three weeks) should be noted, combined as it was with testosterone propionate as advocated by Watson and Turner.¹

It is therefore of interest that Sears *et al.*² reported on the administration of only 150–180 mg. of thiotepa in three weeks to a group of patients with breast cancer. They noted regression of tumour in five of six premenopausal cases but in only 24 of 77 postmenopausal cases (personal communication, 1960). These results are remarkably similar to those noted by Drs. Lyons and Edlstein and were achieved with a considerably lower dose of thiotepa. What is, however, even more significant is that Sears *et al.* noted persistent amenorrhoea following thiotepa administration in all the premenopausal cases. Experimentally they showed that in mice atrophy of the ovaries occurred following administration of thiotepa to marrow toxicity levels.

There is therefore little doubt that in the premenopausal patient thiotepa dosage to marrow tolerance causes damage to the ovaries and possibly to other endocrine organs apart from a direct effect upon tumour cells. Its use may even be considered as a "chemotherapeutic castration" in such cases.

In the U.S.A. the Surgical Adjuvant Chemotherapy Group³ has recently published preliminary results in their controlled trial of the use of 60 mg. thiotepa at mastectomy for breast cancer. They note an increased recurrence-free rate in treated cases which is considerably more marked in premenopausal than in postmenopausal cases. It seems likely that this difference can be ascribed, at least in part, to a cytotoxic action of thiotepa, even at this dosage, upon the ovaries or other endocrine target. Nevertheless, this can be only a part of its action, because Gurling⁴ showed objective improvement from thiotepa administration in 10 out of 18 breast-cancer cases recurrent after hypophysectomy. This is a stage where in my experience response to any form of hormone manipulation is extremely rare.

(2) Another conclusion of Drs. Lyons and Edelstyn specifies, "We have been unable to note any relationship between the clinical outcome of treatment and the dose of drug administered or the marrow depression induced." If their observation is significant, this means that similar benefit could have been obtained with a reduced dosage and possibly with a lower mortality. This conclusion is confirmed by an almost identical degree of benefit in the series of Sears *et al.* referred to previously, where a considerably lower dose of thiotepea was used.

In addition, a lack of correlation between thiotepea dose, toxicity, and clinical response in cancers of the breast and ovary is noted by such experienced observers as Wright *et al.*,⁵ Alpert,⁶ and Ultmann *et al.*⁷ The observations made by Drs. Lyons and Edelstyn therefore further confirm the opinion I expressed in recent correspondence (October 27, p. 1128), "In the case of moderately chemosensitive tumours such as carcinomas of the lung, breast, or ovary, increasing the dosage (of alkylating agent) beyond the generally accepted safe level of dose or toxicity is unnecessary as it does not appear to increase the percentage of cases palliated."

This point is not academic, as shown in the following table summarizing the available published results of the Watson-Turner technique:

Author	Toxicity		Objective	
	Deaths	Cases	Benefit	Cases
Watson and Turner ¹	..	0/23	22/23	++
Cree ⁸	..	0/11	10/11	++
Rider ⁹	..	7/11	3/11	
Lyons and Edelstyn	..	5/46	17/46	

++ Oophorectomy added in premenopausal cases.

Considering that the technique is identical in all series, the variation in the proportion of deaths from toxicity is very surprising (varying from 0% to 63%). Like others, I was encouraged to use higher doses of thiotepea combined with testosterone propionate following the publication of Watson and Turner's report in 1959. Because of my experience with the agent previously, I restricted my thiotepea dosage to 90–150 mg. in two weeks but used the full testosterone propionate dosage recommended. As reported elsewhere,¹⁰ deaths from toxicity occurred in two out of nine cases. Like Rider, therefore, I am frankly amazed at the absence of toxic deaths in the first two series given twice the dose given by myself. (One wonders if the well-recognized instability of thiotepea left too long in solution may be responsible for such differences in the incidence of deaths from toxicity.) I strongly urge that in the case of breast cancer, at least, there is no justification for the dose of thiotepea suggested by Watson and Turner. As good a proportion of regression can be achieved by lower doses of thiotepea (seven out of nine cases in my series). A maximum dose of 2 mg. per kilo in two weeks should be given and then only in the absence of bone or liver metastases or a history of recent x ray or chemotherapy administration.—I am, etc.,

Melbourne C.1, Victoria,
Australia.

BASIL A. STOLL.

REFERENCES

- 1 Watson, G. W., and Turner, R. L., *Brit. med. J.*, 1959, 1, 1315.
- 2 Sears, M. E., Eckles, N., and Kirschbaum, A., *Proc. Amer. Ass. Cancer Res.*, 1960, 3, 150.
- 3 Surgical Adjuvant Chemotherapy Group, Progress Report 14, March 1, 1962.
- 4 Gurling, K. J., *Brit. J. Cancer*, 1959, 13, 168.
- 5 Wright, J. C., Golomb, F. M., and Gumpfort, S. L., *Ann. N.Y. Acad. Sci.*, 1958, 68, 937.
- 6 Alpert, L. K., *ibid.*, 1958, 68, 1072.
- 7 Ultmann, J. E., Hyman, G. A., and Gellhorn, A., *ibid.*, 1958, 68, 1007.
- 8 Cree, I. C., *Brit. med. J.*, 1960, 2, 1499.
- 9 Rider, W. D., *ibid.*, 1960, 1, 1501.
- 10 Stoll, B. A., and Matar, J. H., *ibid.*, 1961, 2, 283.

Perinatal Mortality Survey

SIR,—Dr. J. W. MacLeod (December 8, p. 1540) states, "It is not unfair to say that the Royal College of Obstetricians and Gynaecologists would like the G.P. out of obstetrics altogether."

Unfortunately the statement is unfair because it is false. The mistake Dr. MacLeod has made is the more unfortunate because he practises in the region which pioneered the concept of area departments of obstetrics and gynaecology, in which general-practitioner maternity units have played a role of increasing importance. In designing practitioner units the regional board has acted throughout in accordance with the guidance given by the Royal College on the National Maternity Service. Last year in the Oxford Region 6,000 mothers were delivered in these general-practitioner units with no maternal deaths and an uncorrected combined stillbirth and neonatal death rate of 11/1,000. Since then 33 more general-practitioner beds have been made available and a further 46 are in an advanced stage of planning. The impressive results general practitioners have achieved consistently through the years fully justify expansion of this service and the official policy of the Royal College in encouraging a similar pattern in all areas of the country.—I am, etc.,

The Radcliffe Infirmary,
Oxford.

J. STALLWORTHY.

SIR,—I have just received the numbers of the *B.M.J.* in which were published the summary findings of the Perinatal Mortality Survey and the subsequent correspondence. On the basis of unpublished research I performed in Lancashire some years ago I am convinced that the form of the summary as given to the press is disgracefully unfair to the general practitioner.

This is not the place to go into details, but I will cite a few facts from my investigations which involved looking into every infant death occurring in a population of 300,000 over a period of two years.

I found that over 75% of infant deaths occurred in babies who had never been outside the walls of a hospital. I found that one hospital had 20 midwives and 22 pupil midwives for 100 beds while another had 11 midwives and three pupil midwives for the same number. It was not surprising, then, to discover that preventable deaths in the second hospital were 1½ times as frequent as in the first and that the mortality rate for premature infants in this hospital was higher than the national average in every weight category. In the category for babies weighing over 4 lb. 15 oz. (2.2 kg.) it was over twice the figure for England and Wales.

In my investigations I checked up on the general practitioners also, and there were some cases in which they were to blame, but I did not find many in which their actions contributed to the death of the child. However, I did find that social conditions were vitally important, and in one slum area bad mothercraft and poor homes were decisive in 18% of the deaths. In a neighbouring area, however, these factors were important in less than 4% of the cases.

The result of my investigations convinced me that the main social causes of a high infant-mortality rate (and similarly of a high perinatal mortality) were bad homes and bad hospitals. Contrary to my expectations, when I began the survey I found that bad family doctors hardly existed at all.

I write to defend the G.P. and not to criticize the obstetricians—but the infant mortality rate here (25 per