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.,

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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.,

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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.