mEq/l.). It would therefore seem sensible to attempt to minimize the side effects experienced by the patient by making a special effort to keep the serum lithium in the lower therapeutic ranges. To reduce the peak rise to a minimum the lithium salt should be given in small divided doses at six-hourly intervals. Alternatively the use of a slow release compound might overcome this latter difficulty.

One of the practical problems of determining dosage by serum levels is that flame photometer estimations are only performed at selected centres. In Salford, where the estimations are carried out at only one of the hospital laboratories, we have found by a "split sample technique" that whole blood samples kept at room temperature for 24-48 hours give a valid result. If the serum is separated and kept at 4° C., apart from the duration of transportation, a valid reading can be obtained over a longer period.—I am, etc.,

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REFERENCES

- Schou, M., *Journal of Psychiatric Research*, 1968, 6, 67.
- Baastrup, P. C., and Schou, M., *Archives of General Psychiatry* 1967 16, 162.
- Trautner, E. M., Morris, R., Noack, C. H., and Gershon, S., *Medical Journal of Australia*, 1955, 2, 280.
- Greenspan K., Green R., and Durell J., *American Journal of Psychiatry*, 1968, 125, 512.
- Coppen, A., personal communication, 1967.
- Christodoulou, G. N., *Hospital Medicine* 1968, 2.
- Schlagenhauf, G., Tupin, J., and White, R. B., *American Journal of Psychiatry* 1966, 123, 201.
- Zall, H., Therman, P. G., and Myers, J. M., *American Journal of Psychiatry*, 1968, 125, 549, 1181.

Growth and Cancer

SIR,—I must take issue with a statement made in your leading article on puberty and cancer (26 September, p. 722). Osteosarcoma, although a rather rare tumour, does present in many instances in juveniles, but in a population such as that of England it is equally frequent among the aged on account of the considerable number of elderly persons who have Paget's disease of bone. At least in this city we therefore teach that the age incidence curve of osteosarcoma is bimodal in any race if osteitis deformans is markedly endemic.¹

The ominous histogram of bone cancer mortality related to age² might be anticipated from the shape of incidence curves for osteosarcoma.^{1,3} In a series of 246 sarcomata of long bones in persons under 25 years of age culled from the records of the Bristol Bone Tumour Registry and the London Bone Tumour Panel the adolescent incidence peaks for both sexes are demonstrable, and the peak for females precedes that for males. In this series it may also be shown that this female tumour-incidence precocity obtains for each of three major long bones—femur, tibia, and humerus. Furthermore, the sex ratios of tumour incidence for these three bones correlate well with the sexual ratios of the mean bone volumes given by Vallois.⁴ This and other features I believe show that the aetiological triad of age, sex, and site distribution of osteosarcoma are complementary and reflect the dimorphic patterns of adolescent bone growth and maturation.

There can be no doubt that bone tumours tend to appear at an earlier age in females. This

may be shown for osteosarcoma, fibrosarcoma, and giant cell tumour of bone. However, despite the obvious temptation to relate these sexual differences to bone growth after puberty, it may be that the operative word is "growth" in a broader sense—i.e., non-neoplastic cell proliferation. Hems² has drawn attention to the increased incidence of ovarian and prostatic cancer after puberty. This is also the case for the malignant round cell tumours primary in bone, which are not osteogenic and are probably derived from marrow tissues. Taken in conjunction with the incidence peak of adolescent myeloid leukaemia it may be concluded that body growth may influence the appearance of neoplasms, but will show its effects according to the pattern of development of the tissue in which a cancer takes origin.

You speculate on the meaning of these adolescent peaks of tumour incidence and on the frequency with which similar neoplasms arise in subsequent decades. With osteosarcoma certainly the juvenile peak incidence of the second decade is followed by a compensatory trough during the next decade. A striking example may be cited for osteosarcoma of the tibia. In a large series of nearly 600 proved osteosarcomata there were 46 males and 21 females who developed sarcoma of tibia between the ages of 10 and 19 years. During the next decade there are seven males and no female patients with this bone involved. Through the next 20 years there appear in this series six males and seven females with tumours of the tibia. This clearly shows that, in a given bone growth, growth increases the sarcoma risk, while its cessation leads to a low level of tumour incidence.

At the other end of the life span it is equally noteworthy that the age incidence curve of Paget's sarcoma of bone closely follows that of Paget's disease itself.⁵ In this elderly group the site distribution of tumours becomes influenced by that of the antecedent osteitis deformans, though the effect of bone size is still apparent. Thus it is seen that while growth influences the aetiology of juvenile bone sarcoma, in the mature and senile skeleton other potent factors become operative.—I am, etc.,

C. H. G. PRICE.

Hon. Secretary,
Bristol Bone Tumour Registry.

Bristol.

REFERENCES

- Price, C. H. G., *British Journal of Cancer*, 1955, 9, 558.
- Hems, G., *British Journal of Cancer*, 1970, 24, 208.
- Price, C. H. G., *Journal of Bone and Joint Surgery*, 1958, 40 B, 574.
- Vallois, H. V., *Anthropologie*, 1957, 61, 45.
- Price, C. H. G., and Goldie, W., *Journal of Bone and Joint Surgery*, 1969, 51 B, 205.

Diabetic Ketoacidosis

SIR,—We were interested in the communication by Dr. P. J. Watkins and others (10 October, p. 89) on ketoacidosis provoked by influenzal illness in which there was a striking incidence of hypokalaemia.

We have recently been caring for, and are currently investigating, a young woman aged 17 admitted in precoma whose diabetes appeared to have been provoked by a trivial chest infection. Her routine chest x-ray showed patchy bronchopneumonic changes though she had no respiratory symptoms. Her diabetes was previously undiagnosed, and she presented with marked hypokalaemia, the initial electrolytes being Na 138 mEq/l., Cl 104 mEq/l., K 1.7 mEq/l., CO₂ 18 mEq/l. Blood urea on admission was 39 mg./100 ml. and the blood sugar 654 mg./100

ml. It is interesting to record that she had been previously referred to one of us eight months ago for investigation of primary amenorrhoea.

Despite energetic potassium supplements, initially intravenously and subsequently orally, it was seven days before the potassium level returned to normal. Preliminary investigation of renal function does not reveal any obvious cause for abnormal potassium loss nor was there any antecedent history of vomiting, diarrhoea, purgation, or drug ingestion.

The patient's initial cardiograph showed atrial fibrillation, which reverted to sinus rhythm after a four-hour period of intravenous potassium replacement. This latter finding re-emphasizes the importance, as suggested in your leading article (10 October, p. 63), of treating diabetic ketoacidosis as a medical emergency requiring intensive care facilities and careful patient monitoring.—We are, etc.,

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A. MAHMOOD.

T. HARGREAVES.

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Folate and Vitamin B₁₂ in Epilepsy

SIR,—I should like to reply to Dr. E. H. Reynolds and others (24 October, p. 246). There were 114 patients with epilepsy under observation at the time. The 50 patients chosen were those whose case records covering up to eleven years, often transferred from other hospitals, were the most complete. Although Newcastle accepts a serum folate level from 3 ng./ml. as normal we included some cases with a level below 5 ng. Dr. Reynolds accepted a serum folate level of less than 5 ng. as abnormal. The dose of folic acid given was 15 mg./day in patients with lower levels, 10 mg./day in patients with a level of 4-4.9 ng.

The serum folate level rose in all patients. There was no relationship noted between these levels and improvement in the mental state. There was of course overlapping between the groups showing improvement—for example, there was improvement in the mental condition and in mobility or habits or speech.

There are more problems waiting for investigation as Dr. Reynolds and colleagues point out, but I quote: "we would like to emphasize the importance of treatment with both vitamins."—I am, etc.,

C. NEUBAUER.

Newcastle upon Tyne,

Postoperative Deep Venous Thrombosis

SIR,—Mr. N. L. Browse and Mr. D. Negus (12 September, p. 615) present the most recent in a series of extremely interesting studies in the diagnosis and prevention of deep vein thrombosis.^{1,2}

I would like to raise the question of the clinical significance of radioactive-fibrinogen-proved deep vein thrombosis. Clearly this high incidence of postoperative venous thrombosis is not new, and the