mentioned extracerebral sources, especially under the heavy strain of a marathon race, seem to us a more probable source for CK-BB activity in marathon runners after a race. This also tallies with the observation of Phillips et al. that none of the runners demonstrated any neurological abnormalities after the race. Furthermore, most of the runners also revealed increased heart-type isoenzyme (CK-MB) activities and crossreactivity of CK-MB in radioimmunoassays cannot be excluded as a possible explanation for the observations made by Phillips et al., as they note.

We however, are, more concerned about the occurrence of increased serum CK-MB in most marathon runners after a race. CK-MB has established its value as a highly heart-specific enzyme test. The presence of increased CK-MB together with electrocardiographic abnormalities suggestive of myocardial ischaemia heavily suggests a possibility of myocardial injury. A negative technetium-99m pyrophosphate myocardial scintigram does not exclude the presence of small myocardial infarcts, non-transmural infarctions, or subendocardial lesions, the type of myocardial infarction most common secondary to stroke.[6,7]

It has been suggested that increased catecholamines might cause myocardial damage in stroke[8] and acute head injury.[4] Similar humoral mechanisms could exist during a marathon race and could explain abnormal CK-MB activities after a marathon.[1,9] Normal skeletal muscle can release excess creatine kinase in serum, but this is muscle-type (CK-MM) not heart-type. The hypothesis that endurance exercise increases heart-type/muscle-type isoenzyme ratio in skeletal muscle,[9] the situation peculiar to diseased muscle, remains to be proved before transient rhabdomyolysis from skeletal muscles can be regarded as an alternative source of increased CK-MB levels during marathon competition.[9]

It seems to us that a marathon race is a heavier strain to heart than to brain and the recent observations of Stansbie et al. in Cardiff marathon runners[10] support our assumption. Furthermore, Stansbie et al. seem to share our concern about the risks when electroencephalographic abnormalities and increased serum CK-MB activities in collapsed runners complaining of chest pain are not taken seriously.

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CIMETIDINE AND COUMARIN THERAPY OF MELANOMA

SIR,—Osband, Gifford, and their colleagues[1,2] have reported successful immunotherapy of tumours in mice with cimetidine, associated with a decrease in suppressor cell levels. During an investigation of coumarin as a macrophage stimulant[3] to replace BCG in the treatment of melanoma, a 34-year-old man with recurrent stage III disease was treated with coumarin 100 mg daily for 6 months. He refused chemotherapy and in December, 1981, there was marked clinical deterioration with increase in his lesions in the right groin, abdominal and chest wall, and left thigh. He had severe abdominal pain and vomiting and was given cimetidine 1000 mg daily. There was rapid clinical improvement, and within 14 days his lesions had almost completely regressed and he was back at work full-time. He remains in remission (July, 1982) with residual oedema of his left leg due to previous block dissection. Before cimetidine his lymphocyte count was $1 \cdot 4 \times 10^9$/l (T cells 59%, helper cells 31%, suppressor/cytotoxic cells 30%, DR cells 11%) and 14 days later his lymphocyte count was $1 \cdot 5 \times 10^9$/l (T cells 42%, helper cells 26%, suppressor/cytotoxic cells, 18%, DR cells 30%).

In February, 1982, a 45-year-old man and a 72-year-old woman who had been on treatment with coumarin 100 mg daily for several months were given cimetidine 1000 mg daily. Both had progressive advanced disease with liver enlargement and spreading skin lesions. One had lung metastases and had received previous chemotherapy and radiotherapy. Within a week of the start of cimetidine there was marked regression of liver and skin lesions and both patients are now well and in remission on continued treatment with cimetidine and coumarin, although the lung metastases are still visible on X-ray (July, 1982).

In March, 1982, a 35-year-old woman with axillary recurrence from a melanoma (Clark IV) on the back was given both coumarin 25 mg and cimetidine 1000 mg daily after a block dissection of the axilla. There was rapid recurrence and spread of tumour within 14 days, affecting the axilla, chest wall, and lung. She died 5 weeks later.

Further studies are required to explain the surprising results achieved by the addition of cimetidine to previous coumarin therapy and the possibly unfortunate effect of starting cimetidine with coumarin.

Dr Denis Reen at Our Lady's Hospital for Sick Children kindly estimated the T lymphocytes in the first case.

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HORMONES AND FLUID RETENTION IN CIRRHOSIS

SIR,—Your June 12 editorial notes that the extent of the contribution of the renin aldosterone system to the pathogenesis of ascites in cirrhosis remains undefined. Analysis of the data of P. Y. Wong and colleagues (*Gastroenterology* 1979; **77:** 1171) may help to clarify the issue. These workers studied the response of plasma renin (PRA) and aldosterone to the infusion of saline or albumin in cirrhotics with ascites in a stable nutritional and metabolic state. Calculations based on their published data show that PRA and aldosterone (ALD) correlate well:

Albumin infusion.—Cirrhotic: ALD = 20·6 PRA + 154·5 (r = 0·96). Normal: ALD = 2·21 PRA + 28·5 (r = 0·98).

Saline infusion.—Cirrhotic: ALD = 16·26 PRA + 81·4 (r = 0·98). Normal: ALD = 6·90 PRA + 34·6 (r = 0·99).

The slopes of these regression lines were steeper in the cirrhotics than in the controls—i.e., if the steady state in the cirrhotic is disturbed by the infusion of albumin or saline, then, for any change in PRA, the corresponding change in aldosterone is several times greater than normal.

When, however, natriuresis is induced by immersion in water, the slopes of the lines linking PRA and aldosterone are similar in cirrhotics and in controls (Epstein M, et al. *Circ Res* 1977; **41:** 818–29). Immersion increases the central blood volume, the product of the circulation time and the cardiac output. When these factors are measured separately, the circulation time does not appear to change upon immersion while there is an increase in cardiac output (Arborelius MJR, et al. *Aerospace Med* 1972; **43:** 592–98). The natriuretic effect of immersion in water is therefore presumably attributable to an increased cardiac output.

These data suggest that the renin aldosterone system in patients with cirrhosis responds differently from normal to a saline challenge or to modification of the colloid osmotic pressure of the plasma, but similarly to normal patients to modifications in cardiac output. The extent to which these contribute to fluid accumulation in cirrhosis is likely to vary in different patients.

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