Jogger’s blockade

The current fashion for jogging, marathon running, and similar forms of sustained exercise must mean that among the population of tiro athletes will be many who are taking regular drug treatment. Undeterred by the ever-increasing documentation of physical disabilities incurred by jogging and irrespective of the lack of any proof from prospective trials of cardiovascular benefit, many patients with mild hypertension and even ischaemic heart disease seem to believe that running will prolong their lives.

Beta-adrenoceptor-blocking drugs have achieved wide acceptance as first-line drug treatment for hypertension and angina. How far this treatment limits exercise capacity is an interesting question,1-4 as is the corollary—the effects on exercise capacity of the various ancillary properties of beta-blockers, such as cardioselectivity, membrane-stabilising activity, and intrinsic sympathomimetic activity. Most studies have concerned healthy volunteers given a single dose of beta-blocker and then exercised in the laboratory in constant conditions. Extrapolation from these circumstances to the patient with cardiovascular disease exercising on a cold evening presents problems, so that much of the data must be interpreted with caution.

Beta-adrenoceptor antagonists might affect exercise capacity by several distinct mechanisms. Firstly, they depress total cardiac output through antagonism of cardiac beta1-adrenoceptors. Secondly, they might impair the supply of blood to the muscles by their ability to block beta2-adrenoceptors in the walls of the blood vessels. Thirdly, they affect the metabolism of fatty acids, glucose, lactic acid, and insulin. Fourthly, beta-blockers may possibly have a direct effect on muscular contraction—a confusing topic on which a recent review by Professor Bowman has shed considerable light.5 The salient facts appear to be as follows.

Adrenoceptors do mediate a direct effect of catecholamines on both fast-contracting and slow-contracting muscles, and these receptors are of the beta2 type. Whereas in general beta1-adrenoceptors (for example, in the heart) are directly innervated by noradrenergic fibres, beta2-adrenoceptors (for example, in the airways and blood vessels) have no direct innervation and respond mainly to adrenaline released from the adrenal medulla. Beta2-adrenoceptors in skeletal muscle appear to fall into a similar category—as is shown, for example, by the common adverse effect of muscular tremor when inhaled beta2-stimulants are used to treat asthma. Strong emotion is also associated with pronounced tremor (though the part played by beta2-adrenoceptors in Parkinsonian tremor is less clear: while beta-blockers are widely used in the management of essential tremor, they are less useful in the treatment of the tremor of Parkinsonism). As Bowman indicates in his review,6 the pharmacological basis for the effect of adrenoceptors on muscular function may be even more complex. Adrenaline has effects on muscular sodium-potassium membrane pumps, and may also, via cyclic adenosine monophosphate, alter protein synthesis within the muscle fibre. Beta-blockers, by virtue of their membrane-stabilising action, may affect neuromuscular activity at the motor end-plate, and this may contribute to muscular fatigue.

Leaving aside these complex pharmacological niceties, clinicians are well aware that beta-blockers do indeed impair their patients’ exercise performance. Opinions are divided, however, whether one subgroup of these drugs is worse than any other. I am not aware of any reliable comparisons of the relative effects of beta-blockers with and without membrane-stabilising activity (for example, propranolol with sotalol). Comparisons are available, however, of non-selective blockers (that is, those blocking beta1-adrenoceptors and beta2-adrenoceptors), such as propranolol and oxprenolol, with selective blockers (that is, those blocking beta1-adrenoceptors), such as atenolol and metoprolol.

Theoretically, beta1-selective blockers might be expected to have an advantage, but even in single-dose studies in volunteers their expected advantage has been hard to substantiate. Both Pearson and his colleagues from Nottingham,1 and Anderson and colleagues from Sydney, Australia,2 showed that 80 mg of propranolol had a similar detrimental effect to 100 mg of metoprolol on both the endurance of exercise and its perceived severity—how tired the volunteers felt.

The effects of 80 mg propranolol and 100 mg atenolol were compared in a further study on volunteers and the results related to muscle fibre composition.3 Individuals with a high percentage of slow-twitch fibres (those concerned with sustained exercise performance and relying on oxidative metabolism to produce energy) ran faster on both occasions than those with a high percentage of fast-twitch fibres (which are concerned with explosive exercise and rely on glycolytic pathways for energy). Propranolol impaired the performance of the persons with a greater proportion of slow-twitch fibres in their leg muscles more than did atenolol—leading the authors to the conclusion that cardioselectivity may be important to joggers who, by virtue of training, may develop a greater preponderance of slow-twitch muscle fibres. This is an interesting conclusion in view of the similarities of adrenoceptor innervation of fast-twitch and slow-twitch fibres.4

Athletes recognise this adverse effect of beta-blockers and some, even those who are medically qualified,5-allow themselves the luxury of withdrawing treatment before exercise. Clearly, if exercise is taken regularly such action is incompatible with sustained treatment. Which class of beta-blockers is more contraindicated is by no means clear. At present patients who
The hyperkinetic child: two views

For many years British child psychiatrists and paediatricians have been puzzled by the apparently considerably higher incidence of the hyperkinetic syndrome in children found by North American clinicians. Behaviourally defined, the syndrome includes motor restlessness (overactive, fidgety behaviour), distractibility, impulsiveness, and excitability. It is at least four times commoner in boys, starts early in life, and is often accompanied by difficulties in learning and antisocial behaviour. In North America between 5%, and 20%, of primary school children seem to be affected, and the syndrome is diagnosed in up to half of children referred to child psychiatrists.1 In Britain, in contrast, the diagnosis is made in only 1-2%, of children within the normal range of intelligence seen by child psychiatrists.2 Are these considerable differences a result of different diagnostic criteria or categories, differing rates of referral to specialist clinics, or different beliefs about the efficacy of stimulant drugs, or do they reflect a real difference in incidence, perhaps due to environmental influences?

The scientific approach to these questions would require comparisons of American and British diagnosticians rating case histories and observing videotapes of the same children, but no such study has been carried out—though such a project has considerably clarified diagnostic differences in schizophrenia.3 Recently, however, Rutter and his colleagues have reported two studies, one clinical and one epidemiological, showing that the broader concept of the hyperkinetic syndrome put forward by American paediatricians and psychiatrists cannot be sharply differentiated from what would in Britain be called conduct disorder.4 Nevertheless, there appears to be a narrower concept of “pervasive” hyperactivity, which may be distinguished from other clinical syndromes.5 This view is based on a further analysis of data from the survey of 10-11-year-old children living in the Isle of Wight in 1964 and followed up in 1968. A “hyperactivity” factor was extracted from questionnaires administered to parents and teachers. Children rated as hyperactive in one setting only (situational hyperactives; 14%, of the total population) were distinguished from pervasive hyperactives (hyperactive both at school and at home; 2%) on several factors.

Pervasively hyperactive children were of significantly lower IQ on the non-verbal scale of the Wechsler Intelligence Scale for Children than both situationally hyperactive and non-hyperactive children. They were also of lower social class, but the difference held good even when social class was controlled for. In all social-class groups the pervasively hyperactive children had lower cognitive scores. Especially when pervasive, hyperkinesis was associated with conduct disorders but even so only half the pervasively hyperactive group were rated as having any other disturbance, so that the narrower concept of the syndrome certainly could not be equated with disorders of conduct. Furthermore, follow-up showed that persistent behavioural disturbance was associated with pervasive hyperactivity even in children of normal intelligence. For children who had emotional and conduct disorders at 10 years who were not hyperactive the prognosis was good: the disorder persisted into adolescence in only one child in 10. Of the pervasively hyperactive children with conduct or emotional disturbances, in contrast, these problems persisted into adolescence in 80% of cases and in 47% of the situationally hyperactive children.

Hence there seems to be a small but important group of children who are hyperactive at home and at school, who have a high rate of general behavioural disturbance, appreciable cognitive impairment, and a poor prognosis in adolescence. The poor prognosis is, moreover, a function of their hyperactivity rather than their conduct or emotional disorder. Despite the limitations of this study—the children were not examined clinically, cognitive tests were administered to groups and not individuals, and the children were past the peak age for hyperactive behaviour—it helps us to understand the differences between British and American findings.

Treatment cannot be based on a sound understanding of aetiology.6 Some evidence exists for a genetic (possibly temperamental) contribution, for structural or physiological brain abnormalities (for example, defects of arousal), for toxic or allergic reactions,7 and for combinations or interactions with family factors including maternal depression, early deprivation, and poor family organisation.

Pervasively hyperactive children of school age respond well to treatment with stimulants, but in younger children the effects are less certain. Reviewing 110 studies, Barkley concluded that three-quarters of hyperkinetic children given amphetamines or methylphenidate improved, while a quarter did not change or became worse.8 The rationale for this treatment is far from clear, but cortical inhibitory systems are thought to be stimulated by these drugs, and certainly severely affected children improve in concentration and their control of impulsive behaviour.

Stimulants seem generally safe—the side effects of insomnia and suppression of appetite and growth can be controlled by restricting administration to the daytime and by holidays from the drug. Some children, however, do become depressed and apathetic during treatment and a few are quite severely adversely affected. Virtually no reports have appeared of amphetamine addiction or dependency or of other long-term adverse effects,9 and in some children the therapeutic effect is instant and dramatic. The drug of choice is methylphenidate 5-40 mg in two daily doses. Imipramine has also been reported to be effective but is more toxic. Drugs are not panaceas, however, and need to be combined with other treatments if their short-term impact is to be maintained, for they appear not to affect outcome otherwise. The results of trials of various behavioural techniques with and without drug treatment have been promising,10 11 and these methods are probably more effective in controlling hyperactivity, whereas drugs have a greater impact on attention and impulsive behaviour.