The title The New Science of Exercise requires a little explanation. This is an era where exercise physiology appears the domain of anyone and everyone including physiologists, the trainer of the successful Wallabies of the 1991 World Cup, the veterinarian selling steroids to the owners of greyhounds, racehorses and putative Olympic champions, the media and the public at large. Given this societal mix of experts there is a growing public ethic of muddled information which demands a scientific body of excellence to provide advice based on good research concerning an explosion of novel questions. Such questions constitute the New Science of Exercise, which ideally demands a multi-disciplinary approach in a novel laboratory setting, namely, the community. But where does the Australian Physiological and Pharmacological Society stand in relation to this need?

The community is intensely interested in the question of exercise training. A few years ago I was approached by my neighbours (the HUFPUF club of Merewether) and asked if we could meet and discuss why they should jog, and assuming it was good for you, contrive a plan to prove it! And well might they think exercise is good for you. The latest data concerning factors contributing to coronary heart disease risk in men and women (Table 1), and concerning a meta-analysis of the psychological effects of exercise from McDonald & Hodgdon (1991), suggest that substantial benefits accrue from aerobic exercise, particularly when it is noted that exercise itself may improve eg, blood pressure, blood lipid profiles and weight. When we met I told them about risk factors, a little physiology, and something about data collection and graphmanship on their refrigerator door. We devised a detailed protocol which was implemented at 6.30am as a group for three days per week. Each partner set personal goals, and agreed not to compete, but agreed to walk or jog within his/her capability, and to measure the other variables (to keep the other honest) and to document the data on charts and questionnaires over four weeks, including, at the group’s request, information on sexuality (which was not clearly defined). An example of the data is shown in Fig. 1. This is a chart from one woman. The filled circle is her preplotted weight goal: she reached her weight goal and there was a training effect on her waking heart rate. In summary, on average the men lost one half stone (in their language) over the four weeks and had a significant fall in waking heart rate. The women also lost one half stone on average, and there was a trend downward in heart rate which was not significant. The sexuality outcome was riveting. The men thought their own sexuality was enhanced over the four weeks, and so too was that of their partners. On the other hand, the women thought that their sexuality had not improved, and neither had their partners. There has been much debate about this outcome, with no agreed interpretation thus far. But they agreed as a group that they looked better, felt better, worked better and found out how to monitor their fitness. They also felt that success depended on a user-friendly co-ordinator preferably a GP, or a professional physiologist.

*Presented as the A.P.P.S.Invited Lecture during the 55th Meeting of the Society at Melbourne University, February, 1992
Figure 1 A 48 y.o. female subject in the HUFPUF programme. Effects of 3 days per week jogging plus diet on weight and waking pulse rate.

Table 1 Relationship of physical inactivity to other factors contributing to the risk of coronary heart disease.

<table>
<thead>
<tr>
<th>Individual traits and characteristics</th>
<th>Exposure to external Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>A) Probably direct causal factors</td>
</tr>
<tr>
<td>Sex</td>
<td>Nutrition</td>
</tr>
<tr>
<td>Family History</td>
<td>Cigarettes</td>
</tr>
<tr>
<td>Blood Lipids</td>
<td>Alcohol use</td>
</tr>
<tr>
<td>Other blood factors</td>
<td>Physical inactivity</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Coffee</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Overweight (waist:hip ratio)</td>
<td>Some oral hypoglycaemic drugs</td>
</tr>
<tr>
<td>Menopause</td>
<td>B) Probably indirect associations:</td>
</tr>
<tr>
<td>Tissue-type antigen</td>
<td>Vegetarianism (protective)</td>
</tr>
<tr>
<td>Nonspecific ECG changes</td>
<td>Stressful life events</td>
</tr>
<tr>
<td></td>
<td>Soft water</td>
</tr>
</tbody>
</table>
Our laboratory also supervised a different community study of ambitious proportions at the HCF Fitness Centre in Chatswood, Sydney, to confirm or refute the postulate that a community fitness centre would reduce the risk of heart disease (Brown & White, 1986; Brown, Gazibarich & Husain, 1988). The study comprised two groups of men and two of women volunteer citizens of Chatswood, each having 16-18 members in a cross-over trial, each phase being eight weeks long, with five days free at the cross-over. The protocol included stabilisation of diet as well as an HCF circuit programme with strict, Scout's honour compliance. Examples of the data are not without interest (Fig. 2, Table 2). In relation to arterial pressure, Group 1 (male and female data pooled) underwent the programme, and the regression line showed a significant fall of 6mmHg. Group 2 attended the Centre but did not exercise and did not show a significant change in arterial pressure. Group 1 then stopped exercising and arterial pressure returned to pre-exercise levels over five days, and remained at that level over eight weeks. On the other hand, Group 2 pressures fell significantly before they commenced exercise, and then fell significantly further; all up the fall was by the same amount as in Group 1. However the phenomenon of a falling blood pressure in the case of Group 2 was entirely due to the women in Group 2. The data suggest that this particular group had modified their behaviour either subconsciously, or against the rules, prior to the exercise programme. Whatever the case, I told the Board of the HCF verbally that the Centre in

Table 2 Linear regression analysis of mean arterial pressure (AP) change with respect to time (days) during the 138 days of the study at Chatswood in Group I and Group II males (M) and females (F).

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>n</th>
<th>Regression equation</th>
<th>P Reg. Coef.</th>
<th>AP(S.E.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (exercise)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M+ F</td>
<td>18</td>
<td>432</td>
<td>(\bar{AP} = 97.6 - 0.0853 ) (days)</td>
<td>&lt;0.001</td>
<td>95.3 (1.88)</td>
</tr>
<tr>
<td>M</td>
<td>9</td>
<td>216</td>
<td>(\bar{AP} = 101.1 - 0.0591 ) (days)</td>
<td>0.02</td>
<td>99.5 (2.13)</td>
</tr>
<tr>
<td>F</td>
<td>9</td>
<td>216</td>
<td>(\bar{AP} = 94.2 - 0.1115 ) (days)</td>
<td>&lt;0.001</td>
<td>91.1 (2.27)</td>
</tr>
<tr>
<td>II (control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M+ F</td>
<td>17</td>
<td>323</td>
<td>(\bar{AP} = 97.7 - 0.0350 ) (days)</td>
<td>NS</td>
<td>96.2 (1.50)</td>
</tr>
<tr>
<td>M</td>
<td>9</td>
<td>171</td>
<td>(\bar{AP} = 102.0 + 0.0211 ) (days)</td>
<td>NS</td>
<td>102.9 (1.91)</td>
</tr>
<tr>
<td>F</td>
<td>8</td>
<td>152</td>
<td>(\bar{AP} = 92.8 - 0.0981 ) (days)</td>
<td>&lt;0.001</td>
<td>88.6 (1.98)</td>
</tr>
<tr>
<td>I (control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M+ F</td>
<td>16</td>
<td>352</td>
<td>(\bar{AP} = 97.6 - 0.0232 ) (days)</td>
<td>NS</td>
<td>95.5 (1.16)</td>
</tr>
<tr>
<td>M</td>
<td>8</td>
<td>176</td>
<td>(\bar{AP} = 105.6 - 0.0513 ) (days)</td>
<td>0.03</td>
<td>100.8 (1.81)</td>
</tr>
<tr>
<td>F</td>
<td>8</td>
<td>176</td>
<td>(\bar{AP} = 89.6 + 0.0049 ) (days)</td>
<td>NS</td>
<td>90.1 (1.28)</td>
</tr>
<tr>
<td>II (exercise)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M+ F</td>
<td>16</td>
<td>384</td>
<td>(\bar{AP} = 96.6 - 0.387 ) (days)</td>
<td>0.02</td>
<td>92.3 (1.34)</td>
</tr>
<tr>
<td>M</td>
<td>8</td>
<td>192</td>
<td>(\bar{AP} = 106.3 - 0.0555 ) (days)</td>
<td>0.01</td>
<td>100.1 (1.77)</td>
</tr>
<tr>
<td>F</td>
<td>8</td>
<td>192</td>
<td>(\bar{AP} = 86.9 - 0.0219 ) (days)</td>
<td>NS</td>
<td>84.5 (1.79)</td>
</tr>
</tbody>
</table>

Proceedings of the Australian Physiological and Pharmacological Society (1992) 23(2) 125
Figure 2 Effects of a Commercial Community Fitness circuit training programme on pooled mean arterial pressure (AP) of men and women in 2 Groups (Group I = 9 males average age = 41 yr, 9 females average age = 42 yr; Group II = 9 males average age = 39 yr, 8 females average age = 42 yr) in a controlled cross-over study in the Hospitals Contributions Fund Centre at Chatswood (Sydney, Australia). The mean arterial pressures for Group I = 95 ± 1.8 mmHg; Group II = 96 ± 1.2 mmHg.

Chatswood is so effective that they can charge the local women a large fee and guarantee them a significant fall in blood pressure by simply entering the building. Other data showed significant improvements in lipid profiles, weight loss, flexibility and VO2max estimated by heart rate changes during simple exercise tests to exhaustion. All in all, an interesting and worthwhile evaluation study which confirmed the hypothesis that a commercial fitness programme can succeed, but indicated as well, that you have to keep at it, since the control systems appear quite sensitive over a few days to a switch either way in life style. The study also confirmed what all professional physiologists know. Outside the traditional laboratory setting, that is to say, in the community laboratory, it is doubly difficult to "control" the experimental environment.

The demonstration of favourable effects of exercise on risk factors and well being in community settings, and the hint that the control systems involved are quite sensitive begs the question of appropriate and minimal beneficial stimuli. Postmenopausal women have an added problem of osteoporosis, which is postulated to result in part from ovarian involution and the lack of oestrogen, and perhaps from lack-of-exercise induced strain on, in particular, trabecular bone (White, 1991). On the grounds that a single exercise stimulus might be effective in causing adaptation in the blood pressure control system and, in the postmenopausal age group provoking the adrenal cortex to raise sex hormone levels, the effects of simply walking such people around the University campus ring-road over 3.4 kms in 30 min were studied. In the same people the effects were compared with those of 40 min cycle ergometer exercise at an
**Figure 3** Pooled effects of cycle ergometer and 3.4 km brisk walking exercise on mean arterial pressure in each of 12 men (average age 61 yr) and 12 women (average age 61 yr). The symbol on the left is 2 S.E. of the mean difference between any two time intervals.

Estimated 50% VO\textsubscript{2 max}. The cardiorespiratory and hormonal activity of the subjects were studied over the 6 hr post exercise.

Either stimulus is equally effective on lowering blood pressure in both women and men. The pooled data for men and women, and for each form of exercise, is shown in Figure 3. It shows blood pressure falls by a nadir of 6 mmHg commencing 0.5 hr after exercise, and persisting for about an hour, thereafter returning to pre-exercise levels at 6 hr. These data suggest a single, prolonged bout of exercise does cause virtually instant adaptation of the blood pressure control system, which could represent the baseline for chronic adaptive effects of much longer duration, should repetitive exercise training be involved.

With respect to hormones in the same subjects, men at the age of 61 years have good testosterone and oestrogen levels at rest, and in response to exercise of both kinds show an initial rise, then fall in hormone concentrations which presumably return to pre-exercise levels after some 6 or so hours. By contrast, women at the same age have levels well below pre-menopausal levels, and show no response to exercise effort, say from the adrenal cortex. These results encourage both men and women who are senior citizens, to exercise regularly by walking for reasons of adaptation downwards in their blood pressure. However, while men have normal sex hormone levels at rest and can raise these due to exercise, women have levels which are quite low, and which do not respond to either walking, or cycle exercise. The data also show that the reduction of blood pressure post-exercise is not sex hormone dependent.
Now it is well known that reproductive women will respond to acute exercise by raising oestradiol amongst a variety of other hormones. This was shown eg. by Jurkowski, Jones & others in 1978. The work of Gorski et al., (1976) using swimming rats showed clearly however that oestradiol had a glycogen sparing effect during endurance performance, and in 1986 Wendy Brown suggested this may be to the advantage of women in endurance events eg. the marathon, due to the unique oestrogen/fat link in women coping with their limited CHO stores. A test of this hypothesis was to examine the early levels, and rate of change of respiratory exchange ratio (RER), reflecting the mix of fat and carbohydrate usage, during a two hour cycle marathon in the laboratory. The results predicted were that women trained or untrained burn early in the event a greater proportion of fat than men, due to the presence of oestrogen, and from this starting point, women would have a lesser slope of RER vs time compared to men, who would burn up their carbohydrate more rapidly and move to a greater proportion of fat usage along a steeper RER slope. The data however did not turn out that way (Brown, Walker, White, McGinley & Vining, 1986).

Figure 4 Response of oestradiol (E$_2$) concentrations in 6 highly trained males (open circles; average age = 29 yr, VO$_2$ max = 67.0 ± 1.98 ml.kg.min$^{-1}$), 6 trained males (closed circles; average age = 31 yr, VO$_2$ max = 57 ± 0.97 ml.kg.min$^{-1}$) and 6 untrained males (closed squares; average age = 28 yr, VO$_2$ max = 37.6 ± 2.15 ml.kg.min$^{-1}$) at rest, during 50-60 min graded exercise to maximal effort on a cycle ergometer, and over a 240 minute recovery period. The upper curves show group responses which did not differ one from another; the lower single curve is for pooled data. Vertical bar indicates ± 1 SE Diff between 2 time intervals, calculated by analysis of variance.

Firstly, the RER response of the women (untrained and trained) showed that they were in fact burning more fat than men (untrained and trained), but the slopes were identical. Only supertrained men showed a greater slope. And this was probably because they were physiologically carbohydrate loaded, but even so, their substrate mix after two hr of cycling was the same as in women. The initial hypothesis was thus refuted, unless the males were producing E$_2$ as well. So we got the men back and tested them for an exercise induced hormone response with a somewhat surprising E$_2$ result (Fig. 4).

The data are responses to an initial 2 x 20 min staged exercise effort, then to exhaustion. The data are for untrained men, trained men and supertrained men. Statistically the three responses are the same: for this reason the data were pooled. Of great interest is the high E$_2$
levels at rest, the degree to which they rise, and the post-exercise nadir at four hr after exercise, a response not dissimilar to that for $E_2$, and testosterone for that matter, in the 61 year old men. So that if the hypothesis concerning the link between oestrogen and an enhanced fat usage was true of the females, then it could well be true for the male, and this would explain the RER data. These findings also have a bearing on clinical medicine, and in addition, on control theory in athletes; namely, if it is true that women are relatively protected from heart disease because of their oestrogen/high HDL link, then on the score that exercise of this kind pulses $E_2$ in men (albeit at a lower concentration than in women depending on the phase of their menstrual cycle) here lies a justification for asking men to recreate themselves frequently, in the cause of prevention of atheromatous heart disease.

In terms of control theory, it had not escaped our notice that a proportion of athletic women had a disturbed menstrual cycle, and like men lowish blood pressures and resting bradycardia. A review of the literature in 1987 (White, 1987) showed not only did women have low oestrogen and other sex hormones at rest, but other system indicators appeared down-regulated as well eg, thyroid hormone, and calcitonin. These data together with our own, and other results notably from Jennings at the Baker Institute (Jennings, Nelson, Esler, Leonard & Korner, 1984), showed that controlled training would certainly lower arterial pressure and heart rate, and sympathetic tone. We also knew that during exercise, while arterial pressure rose, the arterial baroreflex was functional and still able to regulate systemic pressure through changes in heart rate and vascular sympathetic tone. These data came from the elegant experiments of Paris, Jamieson & Ludbrook (1982) using exercising rabbits. In these animals systemic blood pressure could be altered during exercise on a treadmill, by controlling the carotid sinus pressure using a preimplanted pressure capsule manipulated through an external lead.

Therefore, if the arterial baroreflex and its central connections were under constant upward strain during exercise, and if this state were imprinted frequently enough ie. in an autonomic memory, adaptation might appear at rest i.e. there would be bradycardia and relative hypotension, and withdrawal of sympathetic tone (White, 1991).

In the same way, the upward and frequent pulses of hormones including $E_2$ would switch off the hypothalamic pituitary axis, resulting at rest in low concentrations of sex hormones, and manifest as menstrual irregularity (White, 1991). This of course does not deny central command may also play a role in directly adapting the controls at rest. But it is curious that the resting patterns of effect resemble the patterns you would expect if the brain and its sensory systems perceived that exercise was persisting even though exercise had stopped.

With this background, the coupling of irregular menstruation and fatigue syndromes in athletes, raises the question of cause. The initial postulates concerning the endocrine disturbance of the female athlete some ten years ago involved the psychological pressures of her training environment, the Frisch hypothesis (Frisch, 1987, that a body fat composition of less than 22% would not sustain the metabolism of oestriadiol), and a decreased sensitivity of the hypothalamic-pituitary system. Of these theories the first may well conflict with the aforementioned psychological benefits of training ie, a resolution of anxiety and depression etc. As to the second and third, ie. body fat problems and a depressed hypothalamic domain, we can learn something from our own data.

We tackled these questions in teenage ballerinas, as putative models of the female athlete, in Hunter Region community ballet schools, which are non-selective and non-elite (Buchanan, White, Walters, Redman, Quail, Cottee & Hennessy, 1992). We used questionnaires, observations during dance, and controlled exercise tests on the cycle ergometer in our Human Performance Laboratory. Each entering ballerina selected a matched non-
Figure 5 Effects of upright cycle ergometer exercise in 14 dancers (D) and in 8 non-dancers (ND) matched for height (D = 161 cm, ND = 161 cm), weight (D = 52 kg, ND = 52 kg), age (D = 15.4 yr, ND = 15.5 yr) and skinfold thickness, on oestradiol/testosterone ratio (E\_2/T).

C = resting control values, S\_1 = 33% VO\_2\_max per 20 min, S\_2 = 66% VO\_2\_max per 20 min, MAX = exercise at exhaustion, R\_15 = recovery at 15 min following cessation of exercise. The symbol is 2 S.E. of the difference between the mean response of D and ND, calculated by analysis of variance.

dancing non-athlete buddy from school as a control of the local environment. Based on strict criteria for menstrual irregularity, 71% of the sample of 34 dancers had irregular menstruation compared with 19% in the 31 controls. This is a high prevalence matched by other studies in more mature high-level dancers, who had a prevalence higher than found in female runners, who in turn, had a higher prevalence than in female high-level swimmers (Sanbome, Martin & Wagner, 1982). Another surprise was their low normal level of fitness, as measured by VO\_2\_max when there was no difference between dancers and controls. Neither were there differences in resting or exercise heart rate, arterial pressure, or ventilatory variables. However, there was a small but systematically greater stroke volume using impedance cardiography (White, Quail, de Leeuw, Traugott, Brown, Porges & Cottee, 1990) at rest and during exercise in dancers, and of course in cardiac output, in view of the similarities in heart rate.

The difficulty in separating the groups on cardiorespiratory grounds was not apparent when it came to the endocrine profile.

Firstly, oestradiol was systematically lower in the dancers than in the controls at rest - with no rise during exercise. There were, however, high, normal levels in both groups.

The opposite was true of their testosterone levels, where the dancers were systematically higher than the controls, providing for a substantially lower E\_2/T ratio in the dancers (p < 0.05) sufficient to account for menstrual irregularity (Fig. 5). Progesterone was raised or normal in the dancers, also.
There was another surprise in the central hormones. Follicle stimulating hormone (FSH) tended to be higher in the dancers than in controls, suggesting the central mechanisms were far from suppressed, and could respond well to the relatively low $E_2$. These burgeoning young women therefore did not have the picture of a suppressed hypothalamic pituitary system as described by Bonen & Belcastro (1978) for the adult running athlete. Since testosterone was high, these data suggest that the underlying cause for the menstrual disturbance in these adolescent dancers was a block at the aromatase conversion point of testosterone to oestrogen.

It follows that if depression of central mechanisms is common to other highly trained adult female athletes, then these findings in teenagers may represent a transition phase of adaptation. Whatever the case, we are currently focussing on the integrity of enhancers of the aromatase conversion process other than FSH ie. we will examine levels of aromatase, growth hormone and insulin-like-growth factor I (IGF$_1$) (Buchanan et al., 1992).

It was also noted that skinfold measurements in both controls and dancers were similar, as were the weights and heights of the subjects in each group, so that these studies refute the hypothesis of Frisch that the endocrine disturbance is secondary to reduced fat stores. Neither do regional ballet schools bring psychological pressures of note, but such an influence on say growth hormone and the ovary remains unresolved. One thing is clear; this form of training causes quite profound adaptation in the endocrine system, but very little, if any, in the cardiorespiratory system, indicating a relatively high sensitivity of the endocrine system, but not of the cardiorespiratory system, to the stimulus of dance.

We are also seeing an increasing prevalence of "fatigue syndromes" in athletes, ie. dizzy spells, loss-of-form, and odd forms of breathlessness during training and competing. Over the past several years, a few such patients have been referred to my clinic in cardiology. These comprise iron men, marathon runners, swimmers and triathletes. It is a phenomenon of both men and women. The literature of course conjectures on many mechanisms, for example, occult supraventricular tachycardia, viral illness and its sequelae, deficient iron stores and anaemia, deranged immune systems plus reactivated (dormant) viruses. It still remains however that the fatigue syndromes of athletes are poorly defined. The fact that anecdotally the descriptions of how they feel are not dissimilar to patients on beta-blockade, has also caught our attention.

As the makers of atenolol, a hydrophilic, cardioselective $\beta$-adrenoceptor blocker which does not cross the blood-brain barrier, ICI summarise the attributes of the drug as being largely side-effect free, particularly when compared with the effects of lipophilic $\beta$-blockers which do cross the blood brain barrier; patients on such drugs (but not atenolol), dream, and suffer mood changes. However, the traditional theory advanced for the fatigue syndromes of $\beta$-blockers relates to their effects on cardiac output: their "fatigue" when it occurs may well be due to depression of cardiac output at rest and during exercise below levels necessary for, in particular, skeletal muscle perfusion. This could also apply to atenolol. This postulate has been difficult to test - due to adscititious effects secondary to invasive cardiac output measurement in man. We explored the problem, appropriately enough, in 45 year old men, employing the Borg scale for an objective identification of fatigue level (Quail, White, Horton, Buxton, Van der Touw & Cottee, 1989). To ensure the scale and other techniques were sensitive enough for our purposes, we tested the reproducibility of responses in a single group of seven closely matched, normal males (although of different work capability) across four separate exercise tests at weekly intervals. The data showed good reproducibility of subjective fatigue estimates across weeks at each workload, and the data are equally impressive for between subjects at each workload. If the "fatigue" is reproducible, then so, too, should the cardiorespiratory accompaniments across the four weeks, and this was so. With this background, in a separate set of matched 45 year old male subjects, the fatigue hypothesis of
Figure 6  Effects of cumulative, staged, cycle ergometer exercise on cardiac output (impedance cardiography) in 6 normotensive male subjects (average age = 41 ± 2.1 yr) in a randomized, double-blind, trial.  PLAC = placebo; TENORM = tenormin (atenolol); CHLOR = chlorthalidone; C = control at rest; WORKLOAD = external cycle ergometer work, kilopond metres min⁻¹.  The symbol = 2 S.E. of the difference between any two data points calculated by repeated measures analysis of variance.  The vertical bars mark the exercise level above which some subjects reached exhaustion earlier than others and commenced recovery.  R5 and R10 = recovery 5 and 10 min, respectively, for all subjects.

Figure 7  Effects of cumulative, staged, cycle ergometer exercise on perceived exertion (Borg scale) in the same 6 subjects shown in Fig. 6.  The data show that despite the cardiac output restriction when on atenolol, the perceived exertion was not affected as exercise effort increased.  Notation as in Fig. 6.
cardioselective atenolol was studied using acute doses of 50mg 24 hr before, then 50mg 2.5 hr before, testing. The effects were compared with the combined preparation of atenolol plus chlorthalidone, (a diuretic), and two placebos - in a randomised, double-blind trial, all within subject.

Sure enough - after breaking the code - the atenolol compounds were seen, as expected, to effectively lower heart rate and arterial pressure at rest and during exercise. Cardiac output was also systematically lowered at rest and during exercise, thus confirming the first step in the hypothesis of cause of fatigue (Fig. 6). However, there was no effect of atenolol on oxygen uptake, nor were there any differences in lactate output when on atenolol. For these reasons, despite the lesser cardiac output, increased fatigue may not be present, on the grounds that the metabolic needs during exercise could be satisfied by increased oxygen extraction from the blood passing through muscle.

Proceedings of the Australian Physiological and Pharmacological Society (1992) 23(2)
In older people with less fit hearts it may be true fatigue would occur with atenolol suppression of sympathetic support. Nevertheless, these data show that reduced cardiac output per se in normal people will not induce exercise fatigue. Curiously, every subject within the double blind protocol when on atenolol declared they felt "tired" and "fatigued" at rest. Which makes us wonder whether even hydrophilic β-blockers which do not cross the blood brain barrier block β-receptors through the portals of the circumventricular organs in the brain, to effect "lassitude", a mood phenomenon, rather than effect "fatigue", which we define as a subjective outcome of supply and demand during exercise. Therefore, is it so the lassitude syndromes of athletes at rest (they feel fine once they get going) are related in whole or part, to low sympathetic "tone" at select circumventricular points in the brain, induced by repetitive training?

**Figure 9** Mean percent effects of upright 75° tilt from horizontal in 3 untrained, and in 3 chronically, highly trained athletes suffering from "dizzy-spells" with and without nausea. MAP = mean arterial pressure; HR = heart rate; CO = cardiac output; TPR = total peripheral resistance; Zo = mean thoracic impedance. Symbol = 2 S.E. of difference between mean responses over 4 min of the untrained, and trained subjects, calculated by analysis of variance. * Asterisk signifies significant difference between group responses at 5% level or less.

Suspected orthostatic intolerance in athletes a priori suggests some untoward adaptation of postural baroreflex control by chronic training. These thoughts suggested the need for a carefully controlled pilot experiment in which three "dizzy spell" athletes were matched reasonably well with three untrained controls. The postural stimulus was evoked by a tilt-table designed in our workshop by Mr Trevor Oldham and myself, which can tilt head-up or head-down at 15° angle separations and at controlled rates of tilt. Figure 8 shows a 17 year old cross-country marathon champion in the Human Performance Laboratory; she is instrumented for impedance measurements of stroke volume and cardiac output (White, Quail, de Leeuw, Traugott, Brown, Porges & Cotte, 1990) at 75° tilt from horizontal. In this study we randomised the sequence of only head-up angles of tilt. In testing the integrity of the rapidly acting parasympathetic and sympathetic controls, we observed the time course of events over the first four min following 75° tilt, documenting how
the subjects were feeling before we progressed later to studies examining tilt angle/response curves.

Figure 9 shows the time course to "steady-state" of response in untrained and trained subjects over four min to an upright 75° tilt. The "steady-state" occurred by the 3rd min in both groups, so for the "angle" dose/response curves we averaged 3rd and 4th min values. It was notable that for the 75° head-up tilt the mean arterial pressure is maintained well in both groups for a similar shift downward in thoracic blood volume (as indicated by the similar mean thoracic impedance rise in each group). However, there were clear-cut differences in the percent rise in heart rate, fall in cardiac output, and rise in TPR (as indicated by the asterisk) between the groups, suggesting a blunting of autonomic mechanisms raising both heart rate and TPR in the athletes. The effects could be explained by a decrease of sympathetic nervous capability overall, and perhaps a decrease in the capability of vagal tone to withdraw. But the outcome result in terms of cardiac output is at first surprising; rather than being worse off with a fall in cardiac output due to pooling, cardiac output is better maintained in the upright posture (Fig. 9). This must be an adaptation of advantage to the athlete as part preparation for action. There were no fainting reactions in any of the subjects.

In addition, each group was tilted, and then exercised over 10 min to exhaustion, and tilted again 0.5 hr later. There were no significant differences in the responses before and after exercise in the athletes, but in the untrained there was a clear-cut difference in the heart rate and TPR responses before and after in favour of a lesser heart rate response, and a greater TPR effect. These data suggest that a single exercise bout (1) rapidly modifies the neural response to postural strain in untrained people, but (2) in trained athletes the repetitive nature of exercise imprints on and adapts the efferent autonomic outputs to produce the adapted response rendering them unresponsive to the acute exercise effects.

Of even greater interest were the reversal of the changes in heart rate and TPR responses at the greatest upright tilt angle in the untrained, and in the TPR response of the trained subjects. There was a tendency for bradycardia and a reduction in TPR, consistent with a relative increase in vagal activity and withdrawal of peripheral sympathetic activity at the greatest postural stimulus at 75° tilt, relative to tilt at a lesser angle. These data suggest a delicate override of the postural baroreflex by a vasovagal response emanating from eg. receptors in the heart. That cardiac output might improve due to this reaction in the upright posture is not novel to our laboratory: this result was foreshadowed as an outcome of reflex effects evoked in postural and blood volume loss situations by Oberg and White (1970) as a result of withdrawal of sympathetic tone and peripheral vasodilatation. This is the first demonstration of the phenomenon in man to my knowledge, as it has not been possible to measure stroke volume and cardiac output with such frequency and accuracy, and without threat of invasion, prior to the emergence of impedance cardiography. If, however, central endogenous opioids play a sensitising role for the induction of highly trained athlete in the emergence of such vasovagal reflexes (Rutter, Potocnik, & Ludbrook, 1987), the intensity of modern training protocols may be accompanied by random, transient episodes of hypotension secondary to postural strain in selected subjects, resulting in "dizzy spells".

This spectrum of techniques allows the documentation of complete postural baroreflex curves for stroke volume and cardiac output around a supine (neutral) point with great sensitivity in man for the first time, but even so requires care. Although non-invasive techniques do not involve the threat of cardiac-catheterisation procedures, emotion can still run high even with careful use of the tilt-table. Good reproducibility with a single person (Fig. 10) can be achieved provided one understands one's subjects, and allows time for them to "settle down". The curves (Fig. 10) show little variation with stroke volume and cardiac output, but certainly an initial head-down angle of tilt will show heart rate rising, rather than falling. If
3 MIN RESPONSE FOLLOWING TILT

![Graph showing the percentage changes in heart rate (HR) and stroke volume (SV) following randomized head-down (negative degrees) and head-up (positive degrees) tilt 3 min after each departure from horizontal (filled diamond = 100%). Broken line = control, initial response. Solid line = response after 25 min rest. SV = stroke volume. Notation otherwise as in Fig. 9.]

repeated later, heart rate will fall with head-down tilt, as might be expected. The explanation relates to emotional adaptation to the environment, and its effects on cardiovascular variables.

So what does all this mean? I would suggest we are entering an era of need for highly trained physiologists to work on a kind of new science of exercise. We have done reasonably well on the complicated issue of the control of the exercise response (Mitchell, 1990). We now need a systematic approach to the effects of persistent exercise on man at rest. This follows the demands of public institutions, sociologists, and epidemiologists, who believe exercise may be good for health. It also follows the need for someone to demystify the symptoms and signs of high level athletes, who carry national banners, and who may be asked to resolve international differences that cannot be resolved by politicians, and who fashion national images and behaviour of millions of people.

To do this we need a broad framework within which we can tackle hypotheses concerning how raised exercise activity can affect, amongst other things, the brain.

Our own particular approach is based on the known anatomical substrate for adaptation, or resetting if you like, of set points of variables which may project ill health. These appear to be the result of chronic stimulation of for example, all the postural baroreflexes arising from the great vessels and the heart, and from inputs that relate to proprioception, pain and temperature regulation. For each of these autonomic and somatic inputs, there is much integration eg. at the brain stem, hypothalamic, thalamic and forebrain levels (Barr & Kiernan, 1983), involving cortical feedback and processes whereby proprioception (dancing on point in ballet) may well adapt efferent outputs to the circulation, and certainly hypothalamic endocrine mechanisms.

To the extent that mature, adult dancers provoke the system with years of a repetitive, input stimulus profile, at once very postural, isometric, rhythmic, and hot, while that for...
The data from the present series of studies support the hypothesis that human behaviour and health is linked to the chronicity of exercise activity. The question arises concerning the degree to which neurohormonal metabolic adaptations to modern intensive training may in sensitive individuals, cause untoward, permanent changes in control systems regulating interalia, blood pressure and fertility.

Olympic 800m runners is disproportionately rhythmic, and that for our long distance swimming champions is horizontal, rhythmic and cold, we can challenge the brain to provide an output pattern which is input specific, or input non-specific. If the output pattern is input non-specific, perhaps central command prevails in autonomic and behavioural adaptation. If on the other hand it is input specific, it would suggest inputs secondary to the exercise response itself determine the output pattern. Therefore symptoms and signs will be specific to different sports, for example, the high prevalence of menstrual dysfunction in ballet.

But surprisingly to some, the new set points of training project ill health occur across an unusual societal spectrum (Fig. 11). Within the exercise ethic of our laboratory we regard the society of sedentary populations at rest as relatively hypertensive, hyperlipidemic, overweight, of poor work capacity, and aggressive, but very reproductive, in the way a tree will flower and reproduce when threatened. At the other end of the scale we observe the human organism trained for unnatural high performance. It tends at rest to be hypotensive, languid, to require enormous stimulation to maintain interest in its goal, and it is infertile; amenorrhoeic if female, aspermic if male. In arriving at this state, the organism appears to break down due to objective failure in some systems which appear more sensitive to the strain of training than others. The symptoms and signs can be psychological eg loss-of-form, fatigue, or they can be of other physiological ilk, hypotension, anaemia, orthostatic intolerance. Somewhere in between we have mankind at his or her best. It would seem society is ready for a physiologist to look at the new science of exercise as these problems will get worse, not better.

I understand that Claude Bouchart at Laval knows of commercial interests ready to genetically engineer their first supermen and women, specifically for Olympic competition. Once the gene profile for the right physiology is identified the technology available will modify and store the superior gametes, bring them together on demand, and incubate them for a price. These human beings can be cloned, and raised generations apart within or without the same family. It is indeed an interesting future ahead; but are we physiologists ready for the New Science of Exercise?
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