of equivalent drugs, approved by an appropriate body, and he would be paid only for this drug if the "E" box is left open.

By this simple means chemists would be enabled to dispense the most economical drug and the doctor's freedom to prescribe whatever he thinks appropriate would not be affected. The national drug bill should be reduced substantially and no patient would suffer. There are very few proprietary drugs which do not have an equivalent drug which has satisfactory bioavailability.

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Oestrogen treatment and endometrial carcinoma

SIR,—Drs A R Feinstein and R I Horwitz (17 September, p 766) state that "your clinically knowledgeable readers" may wish to await further scientific investigation of the postulated association between oestrogen treatment and endometrial carcinoma. However, what are clinically knowledgeable readers to make of the sentence in their penultimate paragraph—"In one group of women, bleeding with undetectable or undetected early endometrial cancer, the oestrogen prescribed as treatment for the bleeding will be associated with the cancer when it later reaches a detectable state"? If they mean postmenopausal bleeding, or undiagnosed irregular genital tract bleeding before the menopause, these are absolute contraindications to any hormone therapy and thus no sane gynaecologist (leave alone a clinically knowledgeable one) would be guilty of prescribing oestrogens to such women.

It must be agreed that the existing case-control studies are inconclusive for reasons such as those mentioned by Drs Feinstein and Horwitz. But there is enough uncertainty, surely, for "judicious restraint" when prescribing oestrogens, coupled with very careful supervision. It would be unfortunate if the restraint which they favour (when assessing claims about oestrogen's alleged carcinogenicity) led to injudicious prescribing; especially if the more worrying findings are eventually confirmed in well-designed prospective studies.

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Exercise-induced asthma

SIR,—We read with interest your leading article on this subject (27 August, p 536) and the subsequent letter from Professor H G J Herxheimer (17 September, p 767) and would like to comment on two points.

You state that different forms of exercise vary in their ability to produce airways obstruction even when the levels of work, as judged by oxygen consumption, are similar. This statement is often made, on the basis of little published evidence. When comparisons of different forms of exercise have been made an indirect measurement of oxygen consumption, such as treadmill setting or heart rate, has often been used or oxygen uptake measured for a part of exercise only.¹ We have published

the results of studies in which we found no difference in the degree of asthma produced by cycling and running when the tests were carefully matched by directly measured oxygen uptake.² It is true that some asthmatics wheeze after they run whereas they do not after riding a bicycle. We believe that this reflects the higher oxygen consumption that is more easily achieved in running than in cycling, where a smaller muscle mass is working.

Our second point concerns the role of hypocapnia in exercise-induced asthma, which was discussed by Professor Herxheimer. This has been studied either by direct measurement of arterial PCO₂ levels or by observing the effects of voluntary hyperventilation and subsequent hypocapnia in asthmatic subjects. Thus McFadden *et al*³ used an elegant partial rebreathing technique to show that hypocapnia had a small effect on airways resistance compared with exercise.

We recently studied 10 adult asthmatics, measuring arterial lactate and PCO₂ levels before, during, and after eight minutes of exercise on a cycle ergometer. The exercise was of sufficient intensity to be classified in Professor Herxheimer's third group—that is, short, severe exercise followed by wheezing after it had finished. The mean O₂ uptake was 93.3 mmol/min (2090 ml/min), mean maximum heart rate 147/min, and mean maximum lactate level 9.08 mmol/l (82 mg/100 ml). The FEV₁ fell on average by 23.3%, being lowest between 5 and 15 minutes after the completion of exercise. Throughout this time PCO₂ values remained remarkably constant, the lowest values in fact being before exercise (mean 4.39 kPa (33 mm Hg)). During exercise PCO₂ rose to a mean value of 4.81 kPa (36.2 mm Hg) and five minutes after exercise the value was 4.52 kPa (34 mm Hg). Individuals did not vary significantly from this pattern.

As suggested some years ago,⁴ we feel that the airways obstruction is related to the liberation of bronchoconstrictor substances, probably modified by sympathetic and parasympathetic discharge. We feel that it is related to the intensity but not the type of exercise and cannot be explained simply by alterations in PCO₂.

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¹ Anderson, S D, Connolly, N M, and Godfrey, S, *Thorax*, 1971, **26**, 396.

² Miller, G J, *et al*, *Thorax*, 1975, **30**, 306.

³ McFadden, E R, *et al*, *Journal of Applied Physiology (Respiratory, Environmental and Exercise Physiology)*, 1977, **42**, 22.

⁴ Seaton, A, *et al*, *British Medical Journal*, 1969, **3**, 556.

SIR,—Dr H G J Herxheimer asserts (17 September, p 767) that asthmatic attacks provoked by severe exercise are caused by a temporary lack of carbon dioxide in the blood and are similar to hyperventilation asthma. Some unpublished results of an investigation carried out in the Department of Physiology at St Mary's Hospital Medical School in 1970 by some colleagues and myself show that this is an oversimplification of the case.

A group of 19 patients, each with a history of bronchospasm induced by exercise, were studied following (1) hyperventilation breathing air; (2) hyperventilation breathing 5% carbon dioxide; and (3) an 8-min exercise period on a bicycle ergometer, the work level being sufficient to produce

lacticacidosis. Lung resistance, end-tidal PCO₂, and venous blood lactate levels were measured in all patients.

Despite their positive history and in some cases reduced peak flow rates recorded in test trials, 10 patients failed to develop a significant change in lung resistance following exercise or hyperventilation on the day of the test. This clearly implicates the importance of additional factors—for example, the presence of allergens or perhaps a low ambient temperature—in determining the response to both exercise and hyperventilation in a proportion of asthmatics. Of the nine patients who did develop post-exercise bronchoconstriction, only one did so in response to both hypocapnic and isocapnic hyperventilation. The remaining eight patients all developed a rise in lung resistance following hypocapnic hyperventilation but not while hyperventilating on 5% CO₂. In no case, however, was the magnitude of the hypocapnic response sufficient to explain the degree of bronchoconstriction induced by exercise.

Several interesting features of the exercise response became apparent during the investigation. The bronchospasm and metabolic acidosis that developed as a result of heavy exercise became more pronounced during the first 5-10 min of the recovery period. In a small group of patients from whom arterialised venous samples were taken the peak rise in lung resistance occurred at the time when the hypocapnia and fall in pH were maximal (some 10 min after the cessation of exercise). Moreover, the time course of the recovery from bronchospasm matched closely that of the recovery from the lacticacidosis.^{1 2} We did not find, however, that breathing carbon dioxide during the recovery period or performing exercise with a bicarbonate-induced alkalosis prevented the bronchospasm. A transient reduction in lung resistance was noted while breathing 5% CO₂, but this is consistent with the known effects of carbon dioxide as a non-specific bronchodilator.

A rise in lung resistance following exercise and hyperventilation breathing air, but not 5% CO₂, was found in four normal subjects, but as with the asthmatic patients the degree of bronchoconstriction induced by hypocapnia was insufficient to account for the rise in post-exercise resistance observed.

Finally I would refer Dr Herxheimer to the paper by Silverman *et al*,³ who compared the metabolic and respiratory effects of running and cycling in patients with exercise-induced asthma. They clearly showed that running produced more bronchospasm but relatively less hypocapnia and lacticacidosis than cycling despite similar oxygen consumptions. This interesting finding would seem to exclude hypocapnia, or indeed any of the physiological consequences of incurring an oxygen debt, as the sole factor in producing exercise-induced asthma.

The attractive explanation of hypocapnia as the cause of exercise-induced bronchospasm is not tenable, but it is possible that the effects of hypocapnia are potentiated by other factors operating during exercise—for example, the release of chemical mediators or some response to the neuromuscular effects of the exercise itself.

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¹ Seaton, A, *et al*, *British Medical Journal*, 1969, **3**, 556.

² Fisher, H K, *et al*, *American Review of Respiratory Diseases*, 1970, **101**, 885.

³ Silverman, M, Anderson, S D, and Walker, S R, *British Medical Journal*, 1972, **1**, 207.

Experimental trial of the tri-cycle pill

SIR,—Dr N B Loudon and her colleagues (20 August, p 487) conclude that their 12-month experiment of tri-cycle pill-taking shows a high acceptability rate in the 196 women taking part, although 89 withdrew.

One assumes that the women were told of possible metabolic side effects from continuous intake of synthetic hormones, including amenorrhoea after stopping the regimen—as also can occur with the 12-week contraceptive injection.

In view of the increasing incidence of post-pill amenorrhoea following the monthly pill-taking regimen would it not have been more ethical in this experiment to have excluded women of parity O?

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* * We sent a copy of this letter to Dr Loudon and her colleagues, whose reply is printed below.—Ed, *BMJ*.

SIR,—In reply to Dr Elliott, the women in the study were given the same information about oral contraceptives as women starting on the standard 21/7-day oral contraceptive regimen.

We are alert to the possibility of post-pill amenorrhoea in all women who stop oral contraceptives. We are in the process of following up the subsequent menstrual pattern of women who stopped the tri-cycle regimen irrespective of their age and parity, but as yet the data are incomplete. Details of subsequent pregnancies in those women who stopped the tri-cycle regimen in order to become pregnant were included in the paper.

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Painless thyroiditis

SIR,—Before a syndrome becomes a disease the natural history of the illness needs to be known. Painless thyroiditis (leading article, 6 August, p 348) is probably often clinically silent, but its course and duration are not usually known. It sometimes starts as subacute thyroiditis (SAT), when scattered granulomas form in the thyroid and parenchymal cells are focally damaged. This syndrome is rarely if ever due to a viral infection. Transient hyperthyroidism may develop at first, but later biopsies have shown lymphocytic thyroiditis, with variable amounts of fibrosis. Out of 108 patients reported by Woolmer *et al* 16% subsequently became myxoedematous. One patient reported by Copperman,² however, still had granulomas in her thyroid when she died of myxoedema coma.

SAT apparently quite often progresses into Hashimoto's thyroiditis and it is now usually considered to be an immune disturbance. A reason for the immune reaction is evident, in some cases. I found concurrent hyperthyroidism in more than 20 cases of sarcoidosis,³ and the serum in three of them contained long-acting thyroid stimulator (LATS) or LATS protector.⁴ Some of these patients had giant-cell granulomas in their thyroids,⁵ and the same lesion was also reported in a patient with sarcoidosis and SAT.⁶ Moreover, Hashimoto's thyroiditis and myxoedema are sometimes found,⁶ and the cellular⁸ and humoral⁹ immunity is raised in this disease.

Sarcoidosis appears to induce SAT and chronic thyroiditis immunologically whenever

the granulomas invade the gland. Although 10% of the population have subclinical thyroiditis,⁸ it is most unlikely that the granulomas in these patients had reactivated a pre-existing inflammatory process. If thyroid biopsies and Kveim tests were performed earlier, and more often, more cases of sarcoid thyroiditis would be diagnosed.

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¹ Woolner, L B, McConehey, W M, and Beahrs, O H, *Journal of Endocrinology and Metabolism*, 1957, **17**, 1202.

² Copperman, I J, *Journal of the Irish Medical Association*, 1968, **61**, 244.

³ MacGregor, G A, *Proceedings of the Royal Society of Medicine*, 1974, **67**, 221.

⁴ Hancock, B W, and Millard, L G, *British Journal of Diseases of the Chest*, 1976, **70**, 129.

⁵ Karlish, A J, and MacGregor, G A, *Lancet*, 1970, **2**, 330.

⁶ Birchall, G, *British Journal of Clinical Practice*, 1966, **20**, 586.

⁷ Caspary, E A, and Field, E J, *British Medical Journal*, 1971, **2**, 143.

⁸ James, G D, Neville, E, and Walker, A, *American Journal of Medicine*, 1975, **59**, 388.

⁹ Rosser, R, *British Journal of Psychiatry*, 1976, **128**, 61.

The perilous skateboard

SIR,—It is highly regrettable that the BBC television programme *Nationwide* should encourage and publicise the dangerous sport of skateboarding with a national skateboard competition.

The evidence of serious injury in those attempting this hobby is at present impression only, but I predict that it will soon amass and label the skateboard as highly dangerous. The skateboard can achieve speeds of up to 40 mph (64 kph) and the skill and fun in its use lies in its inherent instability. Collision with passers-by in public places has already resulted in its banishment from several town centres, but the real danger lies in fractures and soft-tissue injuries to the participants with which the medical profession will have to cope.

It was not coincidence that the *Nationwide* personality detailed to learn the sport and have his progress monitored appeared on television after his first attempt with a torn ligament of his ankle joint. Furthermore, it was not wise to recommend the use of helmets and then to show film of expert skateboarders performing without, though the flimsy helmets are probably insufficient protection and the knee and arm pads recommended will prevent skin abrasion but not bony injury.

The skateboard is dangerous and its use should be restricted to supervised rinks where training can be given.

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Late infection after total hip replacement

SIR,—Your leading article on this subject (23 July, p 213) and the several responses to it lead us to emphasise the need for careful bacteriological studies if meaningful conclusions are to be drawn. It is common practice for surgeons to deal with infected cases last on the list and thus material for examination is often not available until after normal laboratory hours and possibly left until the following day. As a result oxygen-sensitive anaerobes may be lost or chance contaminants multiply to a level at which they

are erroneously believed to be causative of the infection.

In an effort to answer some of the unresolved questions we have removed the bacteriological examination of prosthetic materials from the rest of the routine work and arranged that these specimens are examined as soon as possible after removal. We have also arranged for the examination to include a viable count, under aerobic and anaerobic conditions, of the numbers of organisms present on the prosthesis. As a result we are now able to exclude with some certainty the chance contaminating organism, and anaerobic species have been isolated in sufficient numbers for us to believe they are associated with the breakdown of the prosthesis.

In parallel with this study we are storing sera from patients undergoing major joint replacement. Samples are collected preoperatively and at subsequent outpatient follow-up. This enables us to examine the sera for antibodies by established methods and to develop new techniques for revealing antibodies to organisms isolated by our more searching methods. When late infection is suspected the presence of antibodies in the patient's serum gives a good indication of the time of onset of infection and provides further evidence that the organisms concerned have been involved in the failure of the prosthesis.

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Celiac disease and malignancy

SIR,—It was with great interest that I read the case report of coeliac disease complicated by reticulum cell sarcoma by Drs A P Brooks and Christine I Harrington (17 September, p 739).

We have had a similar case recently, in which, however, there was clinical and histological response to gluten withdrawal. In fact, in our case the morphology of the jejunal mucosa improved *pari passu* with the development and manifestation of the malignancy. At post-mortem examination there was reticulum cell sarcoma in the mesenteric lymph nodes but no involvement of the bowel wall.

It is well recognised that there is an increased incidence of lymphoma and carcinoma of the gastrointestinal tract in patients with coeliac disease,¹ but, although it is generally thought that gluten withdrawal offers some degree of protection from development of malignancy,² this is by no means certain, particularly where lymphomas are concerned.³ Nor does the degree of improvement of jejunal morphology affect the risk of malignancy.

I would disagree with the authors' view that their case is unusual because the lymphoma involved the nodes and not the bowel wall. This seems to be the more usual pattern of lymphomas complicating coeliac disease, whether treated by gluten withdrawal or not, and whether or not the patient shows response to withdrawal. It is the so-called Mediterranean lymphoma that more frequently involves the bowel wall, and in a high proportion of these cases histological diagnosis can be made by jejunal biopsy.⁴ With lymphoma associated with coeliac disease, however, this is rarely the case and recourse to laparotomy is usually necessary.⁵