

It thus seems that temporary lack of CO_2 is the cause of exercise asthma in the same way as it may provoke hyperventilation asthma. However, the mechanism of this is far from clear. There are indications that, in certain conditions, CO_2 may act as a bronchodilator.^{8,9}

In any case, it will be useless to compare various kinds of exercise like running, swimming, or cycling with regard to their wheeze-generating potency without standardising them properly.^{6,10} As pulse-rate increase or O_2 uptake are not the relevant causes of the wheeze, its direct causes—lactic-acid blood level and P_aCO_2 —ought to be used as standards.

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PROGNOSIS OF ASTHMA

SIR,—Your editorial on the age of onset of asthma (Aug. 28, p. 477) quite appropriately points out that bronchial asthma may be caused by treatable "extrinsic" allergens even in the older adult patient. However, the discussion of factors affecting prognosis in asthma is incomplete, since emphasis is made of only two—namely, age of onset and whether the asthma is "intrinsic" or "extrinsic". Most cases of asthma begin in the first five years of life.¹¹⁻¹³ Factors which affect prognosis and determine which children will "outgrow" asthma by adolescence include:

(1) Age of onset: not only do cases beginning in the teens or later have a poorer prognosis,¹⁴ but those beginning in the first two years of life are more likely to have persistent wheezing.^{11,12,15}

(2) Multiple allergic manifestations: hayfever¹⁶ and particularly eczema^{15,17} denote a high degree of atopy and a poorer outlook.

(3) Sex-incidence: while the male-to-female ratio before 10 years is 2/1 and approaches 1/1 by 14-15 years, the severest cases are in males.¹¹

(4) Severity in childhood: this seems to be inversely related to rate of cure.¹⁸

(5) Specific therapy: Johnstone¹⁶ reported that hyposensitisation resulted in resolution of asthma in 72% of patients by age 16 years, compared with 22% in the placebo-treated group.¹⁶ This confirms Rackemann's long-term follow-up study¹⁹ in asthmatic children first seen by him before age 13 years. Flensburg²⁰ found that only 22% of asthmatic children recovered completely, after 6-19 years' follow-up, without specific therapy.

Classification of asthma into "extrinsic" and "intrinsic" categories adds no new knowledge, but merely reflects lack of ability to detect causative factors in certain asthmatics. Except for frequently elevated serum-IgE²¹ in cases of asthma due to multiple allergens, no clear differences in clinical findings, eosinophilia, or allergic family history²² are noted. It is conceivable that food allergy, an important cause of asthma in the young child,²³ might be responsible for the many cases of "intrinsic" asthma reported by

Ford²⁴ in the 0-4 years age-group. Recent evidence has shown that several types of pulmonary immune injury can cause asthma symptoms.²⁵ Careful clinical and immunological investigation might reveal the offending antigen. Elimination of exposure results in dramatic improvement.

The poor prognosis noted in some of the older adults with asthma stems from our inability to determine responsible factors by current allergy evaluation alone. The asthmatic patient should have a complete investigation of food and inhalant allergens, and possible respiratory infection, but also further consideration should be given to type-III hypersensitivity reactions²⁶ in those cases where no type-I reactions can be demonstrated.

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AZATHIOPRINE IN CROHN'S DISEASE

SIR,—You have published two papers^{27,28} on the effect of azathioprine in the treatment of Crohn's disease. In each trial the treatment period was two months. The natural history of Crohn's disease is such that short periods of observation are irrelevant, and it is no accident that one paper finds azathioprine to be effective and the other ineffective. After the 20-year saga of uncertainty about anticoagulants in the treatment of myocardial infarction the lesson about the irrelevance and misleading nature of short-term trials should have been learnt.

A useful prospective investigation of therapy in Crohn's disease probably requires a multicentre trial. The condition is too clinically heterogeneous for clear answers to be obtained either quickly or easily.

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OVULATION SYMPTOMS AND AVOIDANCE OF CONCEPTION

SIR,—Evelyn and John Billings and their colleagues (Feb. 5, p. 282) have made a valuable contribution to contraceptive and fertility techniques with their paper on ovulation symptoms. Clinical observation of the mucus symptoms, although distasteful to some women, does provide an easier and more positive guide to ovulation. But a word of caution is needed. Double ovulation during a menstrual cycle, although not common, does occur, and women being instructed in the ovulation method should be made aware of this possibility. Nor is it enough to say that only those with a family history of twins should be so forewarned. To give an example. A 24-year-old secretary was seen in 1964 with intermittent abdominal pain and discharge. This proved to be occurring at ovulation. The vaginal discharge appeared normal and was not infected, and her cycle length varied from 26 to 34 days. She continued to record the dates of pain, vaginal discharge, and menstruation during the subsequent 12 months. From this record it was noticed that in three separate menstrual cycles double ovulation had occurred about the 12th and 17th days. There was no family history of twins. This woman subsequently had a 16-week spontaneous

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abortion of a biovular twin pregnancy in 1969. The importance of every woman being familiar with and able to recognise and understand her own individual menstrual pattern cannot be too strongly emphasised. This can be achieved only by the regular use of a menstrual chart.

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VASECTOMY AND THE ENDOCRINE
FUNCTION OF THE TESTIS

SIR,—Vasectomy is widely performed today as a simple method for male sterilisation, and in India it is being advocated on a national scale as part of the population-control programme. The long-term effects of vasectomy, particularly on the endocrine function of the testis, have been a source of lively controversy ever since Steinach reported, in the early 1920s, that vasectomy could rejuvenate ageing males. But his hypothesis that vasectomy is followed by Leydig-cell hyperplasia and enhanced secretion of the male hormone, which ultimately lead to striking anabolic and rejuvenating effects, has found little support from subsequent work.^{1,2}

One of the major difficulties in this area has been that the total mass of Leydig-cell tissue cannot be measured directly, since the cells lie scattered among the seminiferous tubules. Any change in the Leydig-cell population has, therefore, been deduced only from routine histological examination and expressed as a rise or fall from the normal. Such visual impressions can, of course, be quite deceptive, particularly when the tubules are degenerating and collapsing after vasectomy. We have now used a histometric point-counting method³ to measure precisely the total volume of Leydig cells and to ascertain whether vasectomy leads to any real change. In a controlled preliminary study on 20 adult dogs the total Leydig-cell volume, before and 8 weeks after vasectomy, was as shown below:

	Vol. of testis (ml.)	Total Leydig-cell volume Relative (%)	Absolute (ml.)
Before vasectomy	9.81±3.3	15.4±1.04	1.58±0.43
After vasectomy	8.02±4.6	25.2±7.0	1.87±0.70

The Leydig cells have increased from 1.58 ml. to 1.87 ml. per testis, on an average. The increase is modest but statistically significant. When expressed in relative terms, however, the change is much more impressive. The Leydig cells, which ordinarily constitute about 15% of the testicular volume, expand to 25% after vasectomy. It seems, therefore, that although some increase in the total Leydig-cell volume does occur after vasectomy, the histological appearance is much exaggerated because of the simultaneous collapse and degeneration of the seminiferous tubules and the shrinkage of the testis as a whole.

To what extent testosterone secretion is actually increased is still not known. If indeed it is increased, then this will add to the attraction of vasectomy as a contraceptive measure. The Leydig-cell increase observed in these experiments and the increased libido felt by many persons after vasectomy (usually considered purely psychological) support the possibility. The exact mechanism for post-vasectomy Leydig-cell proliferation is unknown to us. Is it merely that the blood-flow is diverted from the degenerating tubules to the interstitial cells? Or is there some yet undefined feedback from the seminiferous tubules to the pituitary which affects gonadotrophin secretion?

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THE KVEIM TEST IN CROHN'S DISEASE,
ULCERATIVE COLITIS, AND CÆLIAC DISEASE

SIR,—In 1970 we reported that over half the Kveim tests in a group of 20 patients with active Crohn's disease were positive.¹ The tests were carried out with Commonwealth Serum Laboratories' antigen, kindly supplied by Dr. T. H. Hurley of Melbourne. Since then we have tested more cases of Crohn's disease with both C.S.L. and Colindale antigens, and we have widened the study to include ulcerative colitis and adult cœliac disease. Tests were undertaken on 78 patients: (i) 39 patients with clinically active Crohn's disease who had not been treated with steroids, and in 29 of whom the diagnosis had been histologically confirmed; (ii) 22 patients with ulcerative colitis, 9 of whom were considered to have hæmorrhagic proctitis; and (iii) 17 patients with adult cœliac disease, confirmed in 15 cases by jejunal biopsy.

Two types of sarcoid spleen suspension were employed—Commonwealth Serum Laboratories' antigen batch 004 and Colindale K12 antigen, lots 18 and 19. Both had been validated against Siltzbach Kveim material. The 78 patients had 98 Kveim tests, 57 with C.S.L. and 41 with K12 antigen; 20 had simultaneous tests with both antigens. 6 weeks after injection of the antigen the diameter of any papule present was recorded, and a skin biopsy of all test sites, whether or not a papule was present, was carried out. Histological assessment followed the criteria of Siltzbach and Ehrlich.² All the tests have been reviewed without knowledge of the previous assessment, and the results were almost identical with those initially reported.

Crohn's disease.—On microscopic reading 23 of the 39 patients had positive tests; of 35 C.S.L. tests 23 were positive, with 10 yielding papules 3 mm. in diameter or more, whereas of the 12 Colindale tests only 2 were positive and none produced 3 mm. papules.

Ulcerative colitis.—6 of the 22 patients produced positive tests. Of 13 tests with C.S.L. antigen 5 were positive, and of 15 K12 tests 1 was positive; only 2 tests resulted in a 3 mm. papule.

Cœliac disease.—Of the 17 patients 5 had positive tests; 5 out of 9 tests with C.S.L. antigen, and 1 out of 14 with K12 antigen. 4 of the C.S.L. tests produced 3 mm. papules.

Of the 20 patients who had simultaneous tests with C.S.L. and K12 antigens 8 were positive for the C.S.L. tests, and only 3 were positive for the 20 K12 tests. 78 patients had 98 tests, of which 37 were positive—33 of 57 C.S.L. and 4 of 41 K12 tests. 15 C.S.L. and only 1 K12 test produced 3 mm. papules. 48 of the 98 tests produced no palpable reactions, but 10 of the 48 were nevertheless histologically positive. The size of the Kveim papules in these cases contrasts sharply with that reported in sarcoidosis, where 67% of 212 tests produced palpable nodules 3 mm. or more in diameter.³ It can therefore be said that the majority of the positive reactions in these intestinal conditions are weak, and that only a small proportion produce papules comparable in size with the majority of those obtained in sarcoidosis.

Several contradictory reports have appeared lately on the subject of Kveim tests in Crohn's disease. Mitchell et al.,⁴ using K12 lot 5 as well as C.S.L. antigen, reported 50% positive tests in 74 patients. We¹ reported a similar frequency of positive responses to C.S.L. antigen in 20 patients with active Crohn's disease. On the other hand, Williams,⁵ using K12 antigen lots 18 and 19, reported only 1 positive test in 32 cases. Siltzbach et al.⁶ had negative

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