

COMMENTARY

ISAAC—a hypothesis generator for asthma?

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Last year's *Lancet* conference, *The Challenge of Asthma*, highlighted once again the need for new hypotheses to help to determine the causes of the increase in asthma prevalence in many western societies over recent decades.¹ This trend has occurred in conjunction with a rise in the prevalence of other allergic diseases and is therefore probably attributable to an increase in susceptibility to, or development of, atopy. Epidemiological surveys have established associations with factors such as family size and affluence,² and advancements in the understanding of the maturation processes of the immune system hint increasingly at the potential for early, or even in-utero, factors to influence an individual's atopic status.³ Nevertheless, the environmental determinants of atopy remain largely unknown, and those that are recognised seem to account for little of the observed increase in prevalence.^{4,5}

The first principle in epidemiological investigation of any disease is to describe its occurrence, and comparisons between populations have led to the identification of causes of many diseases. These "ecological" studies take populations rather than individuals as the unit of measurement and, at their simplest, explore spatial or temporal differences in disease rates to identify disease patterns that suggest a hypothesis on the cause of the disease. The likelihood of environmental factors being important in the pathogenesis of asthma is evident from the rapid temporal increase in asthma prevalence.⁶ The possibility of using the spatial distribution of disease worldwide to identify further important risk factors was the primary impetus for the International Study of Asthma and Allergies in Childhood (ISAAC), the first phase of which is reported in this issue of *The Lancet*.

The main obstacles to the investigation of population differences have been the lack of valid and standard methods to measure the prevalence and severity of asthma and other atopic disease. ISAAC was developed to address these issues, and in the first phase of the study self-completion questionnaires were used to collect data on symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema in more than 460 000 children aged 13–14 years in 155 centres in 56 countries. The effects of language and cultural differences on the questionnaire responses were assessed by use of a video-based questionnaire system in addition to more traditional written responses. Hence, despite the many residual potential biases acknowledged by the investigators, for the first time there are standardised data for a spatial ecological study of these disorders in adolescence.

The findings show remarkable consistency between the three allergic disorders within countries with a low prevalence, these tending to be in eastern Europe and

Asia. Strong agreement between questionnaire and video estimates indicates that this uniformity is not accounted for by language effects. This point suggests that these populations have a low level of atopy, an issue that will be assessed objectively by allergen skin tests in the next phase of ISAAC. The external consistency of these findings can be assessed by comparison with the findings of the European Community Respiratory Health Survey (ECRHS). The ECRHS measured the prevalence of asthma, atopy, and hyper-responsiveness by standard methods in adults in 22 countries.^{7,8} Although ECRHS was predominantly a European and Australasian study, Algeria and India were represented in both ECRHS and ISAAC, and the two countries were in the lowest quartile for asthma prevalence in each study. ISAAC reports greater divergence between countries with a high prevalence of asthma, eczema, or hay fever, although those that were the most consistent (the UK, Ireland, Australia, USA, and New Zealand) were all in the highest category for asthma prevalence in the ECRHS study. These independent observations are therefore in keeping with a greater genetic predisposition to atopy in these populations, but genetic constitution alone is unlikely to account for such huge international differences or for the rapid increase in disease within these high-prevalence countries.

The findings from ISAAC are thus broadly consistent with existing data and also provide the basis for the second component of any ecological study—the exploration of patterns and associations between the spatial distribution of disease and various exposures. The weakness of the ecological approach is that exposure and prevalence are measured at the population level, so there is an assumption that all members of one population share the same exposure and the same risk of disease. This is clearly a major assumption, especially in view of the large within-country differences revealed in the study.

Asthma is also very unlikely to be the result of a single cause/effect relation, and in view of the likely complexity of component causes of asthma, purely descriptive studies, even of the magnitude of ISAAC, are of limited value in investigation of causes. In searches for new hypotheses on cause, there must be recognition that risk factors probably differ between countries, and that a component cause that is crucial in one population may have no discernible influence on disease risk in another.⁹ For example, atopy is a consistently important risk factor for asthma in the developed world, whereas in rural Ethiopia it seems, if anything, to protect against asthma.¹⁰ However, any new hypothesis on aetiology has to fit with what is known about the occurrence of a given disease, and ISAAC provides a standardised framework that is much more extensive than anything else available.

Ecological studies have been useful in other diseases to describe differences that at least signal the presence of effects worthy of further investigation. ISAAC might enable such developments for asthma and other allergic disease.

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Catechol-O-methyltransferase inhibitors for treatment of Parkinson's disease

Levodopa is the most effective antiparkinsonian agent available. However, its 1–2 h plasma half-life and the consequent brief rise in brain dopamine mean that the duration of levodopa-induced clinical improvement is short. Within a few years of starting levodopa therapy with the customary two to four doses per day, patients report that clinical benefit wanes at the end of each dose cycle, producing the “end-of-dose” or “wearing off” pattern of motor fluctuations. This effect commonly necessitates taking levodopa every 2–4 h, to produce a more sustained clinical response.

The short half-life of levodopa is a result of the rapid absorption and equally rapid metabolism through decarboxylation by aromatic aminoacid decarboxylase (AAAD) and O-methylation by catechol-O-methyltransferase (COMT). Inhibitors of AAAD (carbidopa and benserazide) are routinely used in conjunction with levodopa and primarily increase the bioavailability, but do not substantially prolong the plasma half-life, of levodopa. Controlled-release preparations of levodopa plus AAAD inhibitor slow absorption and thereby prolong the rise in plasma levodopa. This effect, however, is obtained at the expense of less predictable time to plasma levodopa peaks and decreased bioavailability.

A new class of drugs for extending the duration of effect of levodopa, inhibitors of COMT, is entering the market. Two reversible COMT inhibitors will be available. Tolcapone (Tasmar) has recently been introduced and entacapone (Comtan in the USA,

Relative clinical effects of anti-parkinsonian drugs in patients with motor fluctuations

	COMT-I	CR	DA agonists	MAO-B-I
Daily levodopa dose	↓(30%)	↑(30%)	↓(10%)	↓(10%)
Dose frequency	↓	↓	0	0
Best motor score	0	↑	0	0
“On” time	↑	↑	↑	↑
Dyskinesia	↑	↑	↑	↑

CR=controlled release. DA agonists=dopamine agonists.
MAO-B-I=monoamine-oxidase-B-inhibitors.
↑= increased; ↓= decreased; 0 = unchanged

Comtess in Europe) will soon follow. COMT inhibitors prevent the widely distributed COMT enzyme from transferring a methyl group from S-adenosylmethionine to the hydroxyl group in the 3 position of the benzene ring of levodopa or dopamine. O-methylation of levodopa prevents its conversion to dopamine in the brain; O-methylation of dopamine is one step in the metabolic inactivation of levodopa.

COMT inhibition slows the elimination of levodopa from the plasma (increases plasma half-life) and thereby increases the area under the curve (AUC), but without altering the time to levodopa plasma peak or the maximum concentration.^{1–3} These pharmacokinetic alterations may be an advantage over increasing the dose of levodopa, which also increases AUC but additionally raises peak concentrations, which in turn relate to adverse effects such as dyskinesia. The effects of COMT inhibition also differ from those of controlled-release levodopa preparations, which slow absorption and reduce bioavailability.

Tolcapone differs from entacapone in being a more potent inhibitor of COMT in the periphery and in penetrating into the brain, to inhibit brain COMT as well.⁴ The effects of brain COMT inhibition are less clear; it is not known whether brain COMT inhibition materially affects duration of synaptic action of dopamine. The lack of antiparkinsonian action of tolcapone when given alone suggests that the central effects of COMT inhibition are very small.⁵ The theoretically beneficial effects of reducing the formation of 3-O-methyldopa, a potential inhibitor of levodopa transport into the brain, are probably clinically insignificant.⁶

The pharmacokinetic changes induced by COMT inhibition reduce the daily levodopa dose by enabling a reduction of each dose or an increase in dose intervals (panel). With repeated doses of levodopa every 2–6 h in the presence of COMT inhibition, the mean plasma levodopa concentration is raised and the trough concentrations are increased proportionally more than the peak concentrations despite a reduction in levodopa dose.² Since this “levodopa-sparing effect” does not reduce plasma-levodopa concentrations or, presumably, the amount of levodopa entering the brain, it would not spare the brain from exposure to free radicals formed from levodopa and dopamine, a theoretical concern. As would be predicted by the slowed elimination of levodopa, the duration of antiparkinsonian action with single doses of levodopa is prolonged by COMT inhibition.^{2,3,7}

The dose of COMT inhibitor is not selected by titration. Patients are started on a fixed dose—100 mg

three times daily with intervals of 6 h for tolcapone and 200 mg with each dose of levodopa for entacapone. Tolcapone can be increased to 200 mg three times a day for a modest further increase in levodopa effects. The clinical benefits of COMT inhibition are immediately apparent to the patient. Motor function improves if the patient is a stable responder to levodopa⁸ and time "on" increases if the patient is a motor fluctuator.^{3,9-12} The more "off" time the patient experiences, the more benefit that may accrue from COMT inhibition.¹² Benefit occurs in patients treated with immediate and with controlled-release levodopa.¹¹

The adverse effects of COMT inhibition are largely those of increased dopaminergic stimulation, primarily dyskinesia. The increase in dyskinesia occurs immediately when a COMT inhibitor is given. The physician can anticipate this problem in dyskinetic patients and reduce levodopa at the time of starting the patient on COMT inhibitors. Alternatively, the patient is started on COMT inhibitors early in the working week so that adverse effects can be promptly reported and suitable dose adjustments made. Dyskinesia can generally be managed by reduction in levodopa doses and increase in the dose intervals. COMT inhibitors cause diarrhoea in a few patients and tolcapone may be associated with rises in concentrations of liver enzymes, which have rarely been reason for stopping the drug.^{8,10,11}

How will COMT inhibitors fit into the established armamentarium of antiparkinsonian agents? With one possible exception, they may be used with any of the other agents without adverse interactions. That exception may be the concomitant use of apomorphine, a drug that is a potential substrate for O-methylation. Dopamine agonists and selegiline also extend the effects of levodopa, but by augmenting the action of dopamine formed from levodopa. A limited comparison of the effects of bromocriptine with tolcapone indicated that tolcapone allowed a greater reduction in levodopa dose and increased "on" time more than did bromocriptine.¹³ Like COMT inhibitors and controlled-release preparations, bromocriptine and selegiline may increase dyskinesia. Further experience with the COMT inhibitors will determine their relative strengths and weaknesses compared with other agents but non-comparative studies suggest the relation indicated in the panel. Whatever happens, clinicians will welcome a new class of drugs with a different mechanism of action for relieving the symptoms of Parkinson's disease.

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What risk of infection with IUD use?

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Globally, intrauterine contraceptive devices (IUDs) are used by more women as a method of reversible contraception than is any other. The demographics of use vary widely. Women in the less-developed world constitute the great majority of users, outnumbering those in the more-developed regions by more than seven to one.¹ Almost 70% of all users are in China, where 33% of married women of reproductive age use IUDs. In tropical Africa, fewer than 1% of such women do so; they number a twelfth of the 72 million Chinese users.

The device is highly effective in preventing pregnancy, the effect is reversible, and IUD use is regarded as a medium-to-long-term method of fertility regulation. The drawbacks include expulsion and infection, the former commonly being related to the latter. Most expulsions occur in the first year, and especially in the first 3 months after insertion. Typical expulsion rates for modern devices in the first year range from 1.6 to 8.0 per 100 users.² The risk of infection, presenting as pelvic inflammatory disease (PID), is also greatest in the first 3 months of use. Infection is generally polymicrobial and is associated with a preponderance of anaerobic organisms.³ These organisms can be isolated more commonly from the cervix of IUD users than of women using barrier methods.⁴ The risk of PID is greater for women with multiple than for those with single sexual partners.⁵ IUD users with multiple sexual partners will therefore be at risk of infection at any time after insertion. For parous women with one sex partner, the risk is from bacteria introduced at insertion. The relative risk is six times greater in the first 20 days.⁶

In view of the popularity of IUDs (especially when compared with oral contraception), there is a relative paucity of published work on IUD use, especially of data from the developing world or on use by HIV-infected women. However, two recent papers have addressed the complications of IUD use, and one them has focused on an HIV-1-infected population from a developing country.

The study by Terri Walsh and colleagues⁷ is a large

triple-masked, randomised, controlled trial of 500 mg azithromycin or placebo given at time of insertion to women judged on their self-reported medical history to be at low risk of sexually transmitted infection. The study was well designed, being based on experience in a pilot study. Removal of the device within 90 days of insertion for reasons other than partial expulsion was taken as an indicator of acute or subacute pelvic infection. The secondary outcome measure—postinsertion use of medical services for gynaecological complaints—is known to lead to some under-reporting in this type of trial,⁸ but the use of Hager's clinical criteria for the diagnosis of salpingitis is reassuring.

Rates of IUD removal within 90 days of insertion were almost identical among the treated and untreated groups. They were low and in keeping with reported rates. Few instances of clinically significant gynaecological problems were detected at subsequent visits to clinicians, and rates were similar in both groups. Routine antibiotic prophylaxis at IUD insertion for women in developed countries at low risk of gynaecological infection thus seems unwarranted.

The other report, by Samuel Sinei and colleagues, is published in today's *Lancet* and relates to IUD use among HIV-1-infected women not thought to be at high risk of sexually transmitted infections. Clinicians were unaware of HIV-1 status. The 144 HIV-1-infected and 471 non-infected women in the study were screened for gonorrhoea and *Chlamydia trachomatis* at 1 month. At 4 months only those with symptoms were tested again. Diagnosis of pelvic disease was based on sound and accepted clinical criteria. Use of IUDs was not associated with an increase in short-term complications.

Trials such as these two screen the woman, but not her male partner, for sexually transmitted infection before insertion. Sexually introduced infection after insertion can thus never be discounted but, on the assumption that this did not happen, how do the papers by Walsh and Sinei help in the identification of potential IUD users who would be at low risk of sexually transmitted infection?

Walsh and colleagues used clinician assessment of a woman's self-reported medical history to identify such women. Only 1% had a previous history of PID, mean age around first intercourse was 18 years, and 85% were married or living with a partner. 18% had a previous history of sexually transmitted infection. The Sinei group conducted nurse-led interviews to obtain information on sexual behaviour, and a gynaecological examination was done by a doctor. Only 8% of their HIV-1-infected women had a history of sexually transmitted infection, but one in four had a partner with a possibly sexually transmitted infection in the previous year, and only 67% were married or monogamous or both. One in four had cervical friability and one in five had cervical discharge, classic signs of infection. Both study groups had lower rates of PID and expulsion than have been reported by other investigators.² One conclusion might be that low-risk groups are identifiable clinically. Another interpretation is that the risk of postinsertion infection is lower than generally accepted.

Although not much research has been done into IUD use by HIV-infected women, what there is seems to indicate that the device is suitable for use by these women.⁹ IUDs have not been associated with increasing transmission or acquisition of HIV infection or with accelerating progression of HIV disease. Neither is contraceptive efficacy reduced among HIV-infected

women. However, theoretically, severity of PID in HIV-infected women may be increased and related to their degree of immunodeficiency, and any IUD-related menorrhagia may increase risk of HIV infection for sexual partners.⁹

Many other questions unanswered. Should prophylactic antibiotics be given at the time of IUD insertion in the developing world, where access to health care may be poor? What is the longer-term effect of IUD use in HIV-infected women? Are IUDs an appropriate contraceptive for HIV-infected women with poor access to medical services? When will the problems surrounding contraception and sexually transmitted infections be regarded as involving a sexual "partnership", with the male partner being taken into the risk equation? Until we answer these questions, it seems that a good sexual history and a commitment to follow-up are essential for IUD users.

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Torticollis – what is straight ahead?

Spasmodic torticollis is the involuntary turning of the head on the trunk, sometimes with additional forward flexion (anterocollis), backwards extension (retrocollis), or lateral flexion (laterocollis). Although the cause of torticollis remains unknown and no consistent structural, biochemical, or molecular abnormality has so far been identified, recent psychophysical studies have revealed abnormalities in the way patients with torticollis judge the position of their bodies in space.^{1–3} Most intriguingly patients do not always recognise "straight ahead" in the way normal individuals do.⁴

In an elegant study, D Anastasopoulos and colleagues⁴ asked patients with torticollis to identify "visual straight ahead". Patients had to place a laser spot in the straight-ahead direction on a cylindrical screen in front of them while sitting in a darkened room on a swivel chair with head in a frame that could be rotated independently of the chair. When the head and trunk were aligned (and this meant that patients' heads had to be forcibly positioned in the head frame) both patients and normal controls performed the task equally well and were able to judge accurately what was straight ahead. Patients also performed normally when the head and trunk were rotated together (so that the head and trunk were still

aligned). Patients did not, however, perform normally when the head was rotated on the trunk. Normal individuals reported straight ahead to be close to the mid-sagittal plane of the head although offset by a few degrees towards the trunk. By contrast, patients consistently reported straight ahead to be closer to the mid-sagittal plane of the trunk than to the mid-sagittal plane of the head, irrespective of the direction of their torticollis. In other words, patients with torticollis seemed to relate straight ahead to their trunks rather than to their heads.

Other psychophysical studies have revealed additional abnormalities in the way patients with torticollis judge the position of their bodies in space. Patients have subtle difficulties in recognising when they are in a vertical state (the "postural vertical")² and in recognising when a line is vertical (the "visual vertical").^{1,3} These abnormalities do not seem to be due to the patients' abnormal head position because their performance still differs from that of normal controls who assume similar head positions. The overall conclusion from these studies is that patients with torticollis rely less on the position of their heads than do normal individuals when judging the visual straight ahead, visual vertical, or postural vertical. Such a conclusion implies that patients process the afferent signals from the vestibular apparatus and from proprioceptors in the neck and body in an abnormal way.

The psychophysical studies, by themselves, do not explain the torticollis because all the reported abnormalities are essentially symmetrical, and no correlation with the direction of torticollis has been found. However, the studies are interesting because they are part of a gradual shift in our understanding of torticollis and emphasise the role of postural mechanisms, including the processing of vestibular and proprioceptive afferents, in torticollis.

It may seem self evident, by virtue of the abnormal head position, that postural mechanisms have a central role in spasmodic torticollis, although until recently more emphasis was perhaps given to the abnormal motor activity and muscle spasms, with the condition being viewed as a "movement disorder" rather than a disorder of posture. Other observations also lend weight to the importance of postural mechanisms. Torticollis is most apparent when the patient assumes an upright posture and usually disappears on lying down. It is also commonly associated with a postural upper-limb tremor⁵ and with vestibulo-ocular reflex abnormalities.⁶ Furthermore, behavioural abnormalities have recently been reported in postural neck reflexes elicited by vibration.⁷

The finding of altered processing of vestibular and proprioceptive signals in patients with spasmodic torticollis may also provide the basis for understanding the phenomenon of the "geste antagonistique", in which patients are sometimes able to correct the position of the neck by gently touching the chin or head. Thus a patient with a torticollis to the left may use his right hand to touch the right side of his chin, to make the head to turn rightwards to the primary position. It is presumably the additional proprioceptive information provided by the manoeuvre that restores the head position.

Recent psychophysical studies have therefore provided new insights into the mechanisms underlying torticollis. Patients with spasmodic torticollis make errors in judging the position of their bodies in space. The exact mechanisms responsible for these errors remain to be elucidated. How these errors relate to the torticollis or to

the presumed basal ganglia disorder is also uncertain. Nevertheless, these recent studies have undoubtedly led to an important and conceptually useful re-evaluation of the processes underlying torticollis.

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Training in orthopaedic spinal surgery

Spinal surgery, once mainly the province of neurosurgeons, has become a major subspecialty of orthopaedics, yet in Europe there is no formal training programme for orthopaedic surgeons who want to specialise in spinal surgery. The UK, which comes next to Ireland in having the lowest number of orthopaedic spinal surgeons per head of population in western Europe, might be about to take the lead in Europe with a carefully designed and supervised training programme. Such programmes (accredited by the Accrediting Committee for Graduate Medical Education) have long been available in the USA, but the curriculum varies with the training centre. Some curricula produce only superspecialists (eg, those who focus on specific parts of the spine, or on children).

The need to attract young surgeons into spinal surgery was discussed at the British Scoliosis Society's annual meeting last month. The proposal was for a broad-based interdisciplinary 6-year programme encompassing four modules (degenerative disorders, trauma, tumours, and deformity) and including time in neurosurgery. An essential ingredient of the programme is the recognition of the existing regional specialist spinal units as having the expertise to provide the training. The hope is that final agreement on a programme will be reached by neurosurgeons, orthopaedic surgeons, and others at the Brit Spine 1999 meeting in Manchester.

Having an adequate pool of trained spinal surgeons ought to reduce waiting lists for spinal surgery and hence improve outcome for patients such as infants and adolescents with scoliosis, since the curvature can deteriorate greatly during fast growth. Would there also be a reduction in rate of failed back surgery if there were a common approach to surgical management of back pain that addressed not only disc or nerve damage but also maintenance of spinal stability? The answer can come only from assessment of the programme.

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