COMMENTARY

Albendazole for mass treatment of asymptomatic trichuris infections

See page 1103

Over recent years the mortality of young children in developing countries has been reduced by mass immunisation, but there is no cause for complacency since many currently non-immunisable threats to their health remain. One major, and previously under-appreciated, threat to physical fitness and cognitive development is intestinal nematode infestation. Despite medical advances in other areas, the global prevalence of intestinal infestation by worms is largely unchanging, while the number of cases is rising.[1,2] Recognition that young children carry the heaviest burden of intestinal worms, and appreciation of the consequences, have been accompanied by the availability of cheap and effective drugs, hence the calls for periodic mass treatment of high-risk populations in developing countries.[3]

Trichuris trichiura (the "whipworm") is a common intestinal nematode in tropical countries and is generally accompanied, in the same host, by other parasites, including *Ascaris lumbricoides* and hookworm species. Adult *T trichiura* inhabit mainly the caecum but can parasitise the whole colon. Light infections are generally asymptomatic, but heavy infestation can produce severe clinical illness, including anaemia, finger-clubbing, bloody diarrhoea, and rectal prolapse. The harmful effects of "trichuris-dysentery syndrome" on growth in young children have been reported, as has catch-up growth after effective treatment.[4,5] The effects of asymptomatic *T trichiura* infection are less well understood although, in general, the assumption has been that the infection is relatively benign. In today's *Lancet*, J E Forrester and colleagues report that they had set out to examine the effect of treatment of asymptomatic trichuriasis on the growth of young children (with or without other intestinal helminths). In the course of their work they found what they believe is an unrecognised adverse effect of albendazole on growth.

Albendazole is a broad-spectrum anthelmintic that perturbs tubulin polymerisation in a wide variety of organisms, including trichuris, hookworm species, strongyloides, and ascaris. Its oral bioavailability is low, but its pharmacologically active metabolite, albendazole sulphoxide, reaches therapeutic concentrations in plasma and tissues and is chiefly responsible for the drug's systemic effects (eg, against hydatid disease). Although toxicological findings include weight loss in adult rodents (albeit given high doses over several weeks),[6] albendazole has a large therapeutic index. In human beings adverse effects have been mild and have included gastrointestinal upsets when the drug is used at low dose, and raised aminotransferase concentrations when it is used at higher doses for systemic infections.[7]

Forrester and colleagues have examined three anthelmintic regimens (albendazole 400 mg/day for 3 consecutive days, albendazole 400 mg/day once only, or pyrantel once only), each given for three courses with 4-month intervals. They followed up patients for 12 months after randomisation. For ethical reasons there was no untreated control group. As expected, the 3-day albendazole regimen reduced trichuris intensity by 99%, compared with reductions of 87% and 67% in the single-dose albendazole and pyrantel groups, respectively. Arm circumference increased more with the 3-day albendazole group in the patients with the heaviest trichuris infestation (weight, height, and skinfold thickness were no different). However, in the children with the lightest infestation, weight, arm circumference, and skinfold thickness seemed to be adversely affected by the 3-day albendazole regimen. After careful analysis, but hampered by the lack of control groups, the researchers conclude that asymptomatic trichuriasis, and the 3-day course of albendazole, probably impair growth. What are the implications of this finding on albendazole for mass-treatment programmes?

There is no such thing as a safe drug. It follows that therapy invariably results from a risk versus benefit analysis (by patient or physician but preferably both). Such analyses are starkest when drugs are taken prophylactically, when the risks of the drug must be small compared with those of the disorder being prevented. However, asymptomatic intestinal helminthiasis produces adverse consequences on the health of children, and treatment improves both growth and cognitive function. The findings of Forrester and colleagues must be viewed in this context. The suggestion that relatively high doses of albendazole may affect growth deserves further study, ideally in a trial that incorporates matched control groups. However, it should be remembered that the 3-day albendazole regimen employed by Forrester and colleagues is unlikely to see much use in mass-treatment programmes. Consequently, although the finding provides a reminder to use drugs with caution and may stimulate further research in this area, it should not deter the use of single-dose albendazole in mass-treatment programmes for high-risk populations.

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Can oral β_2 agonists cause heart failure?

Despite concern over the cardiovascular safety of the long-acting β_2-selective agonists in general medical practice, especially in patients with heart disease, comparative data are limited. Cardiac failure could even underline an "asthmatic death" rather than be a terminal event. Another concern with salmeterol has been possible adverse effects on the airways. Detection of these uncommon events requires large numbers of patients. Although Glaxo's randomised, prospective 16-week comparison of salmeterol with salbutamol in 16 787 patients was somewhat reassuring with respect to asthma,[1] it lacked the power to detect, at the 0·05 level, even a four-fold increase in deaths from either drug.[2]

In prescription-event monitoring (PEM), physicians report monthly "any new adverse events, referral to a consultant, or admission to hospital" when they prescribe a newly launched drug. An excess of a particular event in the first month over subsequent months further tends to incriminate that drug. New hypotheses are formulated from PEM data and prospectively studied.

Using the PEM technique, researchers from the Drug and Safety Research Unit and the School of Medicine at Southampton re-examined the safety issue for salmeterol, a long-acting inhaled agent, and of bambuterol, a long-acting oral agent and prodrug of terbutaline.[3] Two cohorts, consisting of 15 407 patients begun on salmeterol between September, 1990, and May, 1991, and 8098 patients begun on bambuterol between February, 1993, and December, 1995, were compared with a control cohort of 12 294 patients begun on the mast-cell-stabilising drug, nedocromil, between November, 1986, and September, 1998. There was an excess of non-fatal "cardiac failure" in the bambuterol group during the first month, and a lower but increased incidence during the second to sixth months, whereas there was no excess in the salmeterol group (see table). Ischaemic heart disease was also commoner in the first month on bambuterol, but not thereafter. The team recommends "caution when prescribing oral β_2-agonists to patients at risk of cardiac failure".

In detailed analysis of the 1022 deaths occurring over 1 year in the salmeterol group,[4] only 73 deaths, or 7%, were judged to be due to asthma, and in these cases, severity of disease and advanced age were held responsible. 12 asthmatic deaths occurred in the bambuterol cohort, about half the proportion of those on salmeterol. Concerns over accuracy of the death certificates prevented detailed analysis, but cardiovascular deaths on bambuterol were "in the same positive direction" as the non-fatal events. Deaths on nedocromil were not reported.

This PEM paper further establishes the safety of salmeterol, but it raises questions over the long-term safety of oral β_2-agonists in a general population. Bambuterol is slowly hydrolysed to terbutaline throughout 24 h by tissue butylcholinesterase. Taken at bedtime, it provides high night-time serum terbutaline concentration, which is very useful for the treatment of nocturnal symptoms. Concentrations of bambuterol are about 40% higher in old than in young adults, but pharmacokinetic studies are lacking in patients with heart failure, in whom it is contraindicated.[5]

Adverse effects

	Nedocromil* (n=12 294)		Salmeterol (n=15 407)			Bambuterol (n=8096)		
	RR	(no)	RR	(no)	p	RR	(no)	p
CF								
Mo 1	1·0	(6)	0·81	(10)	NS	4·41	(31)	<0·001
Mo 2–6	1·0	(12)	1·25	(35)	NS	2·67	(31)	<0·01
IHD								
Mo 1	1·0	(5)	1·32	(12)	NS	2·67	(14)	<0·01
Mo 2–6	1·0	(24)	1·01	(54)	NS	0·67	(12)	NS

**Reference group*
RR=age and sex adjusted relative risk; CF=cardiac failure; IHD=ischaemic heart disease

Was the PEM study a fair comparison? Probably not. It took nearly 3 years to collect the cohort of those patients who preferred, or needed, an oral agent. There were fewer indications for "asthmatic/wheeze" (57·3% *vs* 70·2% for salmeterol) and more "other" indications, such as "dyspnoea, bronchitis, cough, chest infection, emphysema, bronchiectasis" (14·9% *vs* 2·8%).

Was the heart failure induced by bambuterol? There may be a simpler explanation. The salmeterol cohort consisted mostly of patients switching to a longer-acting agent, and those on nedocromil were mostly switching from cromolyn. The bambuterol group was more heterogeneous. With or without asthma, some patients with impending or undiagnosed heart failure may have presented with dyspnoea, cough, or wheeze and received bambuterol, the true diagnosis becoming evident during the first month.

There is another possibility. A peak increase of 25% in oxygen uptake and carbon dioxide production occurs 5 min after 800 μg of salbutamol taken by metred-dose inhaler, when systemic absorption peaks.[6] Remarkably, nearly complete tachyphylaxis develops on maintenance dosing. Could such a metabolic demand produce heart failure or angina in some older patients given bambuterol? Systemic terbutaline causes a surprising increase in cardiac output; 0·25 mg given subcutaneously raises cardiac output by 48% in normal young men.[7]

In contrast to fenoterol or isoproterenol, terbutaline and salbutamol are only partial agonists at β_2-adrenoceptors.[8] When fenoterol and salbutamol were given by metred-dose inhaler in increasing doses to healthy individuals, the increases in heart rate and the QT_C interval and decreases in QS_2I (inotropic effect) and K^+ were more abrupt and pronounced for fenoterol, but still significant for salbutamol. Reports of angina[9] and asymptomatic rhythm disturbances[10] after oral or nebulised β_2 agonists dictate that caution is exercised when exposing elderly people to these agents.

In the failing heart, β_1-adrenoceptors are evidently down-regulated by norepinephrine, whereas activity of β_2-adrenoceptors remains relatively unchanged and these receptors assume increased importance in inotropic and

chronotropic stimulation.[11] In six of 20 patients in advanced congestive heart failure refractory to diuretics and vasodilators, oral salbutamol greatly increased brief episodes of ventricular tachycardia during the first 36 h, and a seventh patient developed atrial fibrillation. In those continuing on the drug for 4 weeks, the favourable haemodynamic effects of salbutamol were undiminished.[12] Although these patients had advanced congestive heart failure, they highlight the risk of arrhythmias posed by oral, subcutaneous, or high-dose inhaled β_2-agonists in diseased hearts.

Although oral β_2-agonists have their uses, the route of choice is inhalation. Physicians should not abandon efforts to teach patients in the older age-groups to use a metred-dose inhaler, with a chamber if needed. Failing this, every effort should be made to rule out cardiac disease before prescribing an oral β_2-agonist.

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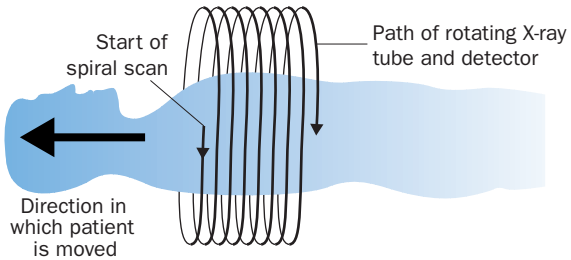
Spiral CT: how much does radiation dose matter?

Even though radiology is a continuously evolving specialty, few people could have predicted the massive resurgence of interest in computed tomography (CT) generated by spiral technology.[1] The advances in magnetic resonance imaging were made with reduction in radiation risk. But the past decade has seen a plethora of publications extolling yet further applications of CT. Importantly, many of these relate to mainstream medical (eg, pulmonary embolus[2]) and surgical emergencies (eg, renal colic,[3] appendicitis[4]). Thus, demand for spiral CT of the chest and abdomen for inpatients continues to rise. But few clinicians realise that CT is responsible for a substantial and increasing proportion of all man-made radiation. In rough terms, about 85% of the radiation burden to the community in a developed country is natural and 15% man-made. Of the man-made sources, about 97% comes from diagnostic radiology, chiefly CT.

Principles of spiral CT



The patient is moved slowly through the gantry during continuous rotation of the X-ray tube. The pitch is the longitudinal distance the patient travels per tube rotation divided by the chosen thickness. For a table movement of 10 mm/s, a tube rotation of 1/s, and a slice thickness of 10 mm, the pitch is 1·0.

Surveys of CT practice[5–8] have consistently shown that the radiation dose from certain CT examinations can be very high; a typical dose for an abdominal CT examination is in the order of 10 mSv (2·3 mSv for a cranial examination). Such an exposure means that one abdominal CT examination carries about the same radiation risk as 500 chest radiographs and a background equivalent radiation time (BERT) of 4·5 years. Relation of the dose to the risk of subsequent cancer is much more controversial and involves an estimation of stochastic risks. On the assumption that the best estimate of risk of fatal cancer to the whole population is 5% per Sv,[9] an effective dose of 10 mSv corresponds to an excess risk of fatal cancer of 1 in 2000. This risk sounds high until put into the perspective of the inherent risk of cancer that everybody carries (approaching 1 in 3). Nevertheless, it calls for frugal use of CT and adherence to national radiological guidelines,[10] and avoidance of repeated CT studies for benign disease in the young patients. Note that, unlike some high-dose procedures (eg, interventional radiology[11]), CT is unlikely to have deterministic effects (ie, those certain to occur when the dose is high enough), because rotation of the source spreads out the entrance dose over a large surface area.

Why is the radiation dose from CT so high? And what steps are being taken to reduce it? The CT image is constructed from many projections, and at each angle the detector must receive sufficient X-ray photons, so CT inevitably imparts higher doses than does conventional radiography because exposure times are longer. Improvement in sensitivity of detectors, anode rating (allowing shorter data acquisitions), and beam filtration have helped to reduce dose. A recent innovation is modulation of the tube current to the patient's geometry and absorption during data acquisition so that no part of the patient receives more radiation than absolutely necessary to produce a satisfactory image.[12] Also, there are now well-established procedures for checking that CT systems are performing optimally.[13]

So why is there continuing concern over doses from CT? All multicentre surveys to date have shown large variations in dose for essentially the same examination.[6–8] Differences in equipment design account for up to three-fold variation in dose, but an eight-fold variation in dose has been found for a paediatric abdominal CT protocol between different centres, and a 14-fold variation was found in a survey in East Anglia,[7] which covered 12 CT

systems in 11 hospitals and 11 different examinations. The tube current (mAs) and total number of CT slices are critical variables. In the abdomen little can be done about mAs (unlike in the chest where perfectly satisfactory images can be obtained with a low-dose technique[14]). The number of slices is determined by the radiologist.

To reduce doses to patients, the UK National Radiological Protection Board[15] has published reference dose levels for all X-ray examinations. These reccomendations are based on data collected in the late 1980s, and it is reassuring to note that, in recent UK surveys of CT practice, mean doses are lower than previously estimated and few examinations exceed the reference dose.[7] It is also reassuring that a standard spiral CT examination (eg, 10 mm thick slices at a pitch of 1·0, see figure) gives the same radiation dose as does the conventional CT examination of old (contiguous 10 mm thick slices) for the same body length covered. Indeed many CT units now routinely use a pitch of 1·5 rather than 1·0 (with very little trade-off in image quality), which gives a theoretical dose reduction for spiral CT. However, spiral CT has opened up many new diagnostic areas, some of which involve a higher radiation burden. For example, an enhanced examination of the liver in the arterial and portal phases[16] may involve several passes of the hepatic parenchyma. Some three-dimensional orthopaedic and vascular applications[17,18] employ a narrow pitch with narrow collimation, again increasing the radiation burden. Above all, it is increasing clinical use of CT that is increasing the collective dose to the population.

Thus, the following are some questions that a clinician (and even a well-informed patient) might ask before a CT examination:

- Can the diagnostic information be obtained by other radiological means at a lower radiation dose? Answer, see Radiological Guidelines.[10]
- Is the CT machine operating satisfactorily? See reports on regular service checks.
- Are the protocols optimum? See audit compared with reference doses.

All these factors will assume even greater importance in the light of impending UK legislation based on a recently revised European Union directive on protection of the patient.[19] Nevertheless, the over-riding fact is that a skilled CT team can provide unique diagnostic information of considerable help to both the referring clinician and the patient.

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Breastfeeding and maternal employment: two rights don't make a wrong

There is plenty of evidence that breastfeeding is beneficial, and the practice has been encouraged by many health-promoting organisations.[1,2] For the mother, the benefits include lower rates of breast and ovarian cancers. For the child, they include lower rates of diarrhoea, otitis media, and lower-respiratory and other infections (which mean that parents need take less time off work to meet their children's needs).[1,2] Furthermore, many babies and mothers, especially after an initial learning period, enjoy breastfeeding tremendously.

Despite these benefits, there is a cost: breastfeeding requires mothers' time, a point that has added fuel to the perennial debate on maternal employment. A recent study of middle-class mothers by S B Fein and B Roe[3] has shown that, among mothers employed part-time at 3 months after birth, duration of breastfeeding was only marginally shorter than that for non-employed mothers, but that it was reduced more substantially among those employed full time. Non-employed mothers breastfed an average of 25·1 weeks, those employed 1–19 h per week breastfed for 24·4 weeks, and those working 20–34 h breastfed for 22·5 weeks ($p>0·05$ for differences). Those working more than 34 h per week breastfed for shorter durations than did those not employed or those employed part-time ($p<0·05$), but still for an average of 16·5 weeks. From these data, the investigators' single major conclusion was that "part-time work is an effective strategy to help mothers combine breastfeeding and employment".

This is one reasonable conclusion. Young children need consistent, loving, and abundant attention, and frequent feedings, and mothers are biologically well suited for and

usually interested in these tasks. Despite this, in the USA where the study was conducted, and where society is said to promote "family values", there are many family-hostile components. In Norway, mothers may receive 100% pay for 42 weeks' maternity leave, or 80% pay for 52 weeks, an arrangement highly conducive to healthy child development. By contrast, the law in the USA stipulates only 12 weeks of unpaid leave. Thus Fein and Roe's findings suggest that employers and families should consider whether mothers would gain from returning to work only part-time.

There are, however, at least four other possible conclusions from these data. First, all of the mothers in the study, irrespective of employment status, breastfed for an average of substantially less than a year, the minimum recommended by the American Academy of Pediatrics.[2] This finding suggests that, apart from employment, there are social, pragmatic, or other factors that discourage breastfeeding.

Second, breastfeeding, particularly after establishment of lactation in the first few months, need not include daytime feedings (although the benefits of breastfeeding are dose related[4]). Mothers can enjoy years of early morning and evening breastfeeding, without daytime pumping or breastfeeding. Availability of suitable written information[5] or of lactation consultants may help parents become aware of such options.

Third, employers can set up potentially mutually beneficial arrangements—eg, by the provision of breastfeeding or breast-pumping breaks and on-site day care, or by the introduction of telecommuting. Fein and Roe are now examining data to evaluate the effectiveness of such strategies.

Finally, although the benefits of breastfeeding are clear, what are the maternal and other costs? As mentioned above, enlightened employer practices can reduce conflicts between full-time maternal employment and day-time lactation. However, to some mothers the cost to their career of daytime breastfeeding or pumping is still too high, especially in the first few months after the immediate postpartum period (when the benefits to the baby are highest)—overnight travel is difficult; colleagues' regard may diminish when they hear of (or hear) the pumping; and the mother may be embarrassed by milk letdown that is copious and uncontrollable. Although some mothers are reluctant to abandon the benefits and joys of breastfeeding, other mothers may decide that despite the benefits babies obtain from mother's milk, the resentment the mothers might feel (especially for extended breastfeeding) offsets the benefits. Women have little choice but to endure the physiological and professional compromises of pregnancy, and may wish to reclaim their bodies and professional stature soon after the birth of the baby.

Breastfeeding and employment are both worthwhile, and both deserve familial, professional, and societal support. Women in this time of substantial life-change should receive such support, irrespective of variability in decisions about how and whether to combine these two valuable endeavours.

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Genetic influences on the age at menopause

The hypothesis that genes affect the timing of the end of reproductive life has been around a long time. There is a strong evolutionary rationale to ideas about the reason for the length of human female reproductive life (and also the reason why the postmenopausal phase in women is longer than that of females of other species). The end of reproductive life is of considerable interest for diverse reasons—not only because women may wish to postpone or prolong childbearing. Evolutionary biologists, demographers, and biometricians have an interest in describing and predicting fertility trends. Obstetricians, gynaecologists, endocrinologists, and associated scientists are interested in furthering options for individual and general fertility. Epidemiologists and statisticians look for predictors of fertility, and for factors that reduce fertility. Genetic epidemiologists can enhance the value of epidemiological research by incorporating information about genetic differences in risk into accurate statistical prediction of the time of menopause.

The paper by Harold Snieder and colleagues from the Twin Research Unit at St Thomas' Hospital, London, is the first to identify a substantial proportion of variance of age at natural menopause attributable to genetic influences.[1] The investigators used twin data to assess the reasons for individual differences in age at natural menopause, in history of hysterectomy, and in two particular indications for this operation (namely, uterine fibroids and menorrhagia). They were also able to assess the phenotypic relation between age at menarche and age at menopause, and they found no significant correlation. The samples of twins used for their analyses were subsets of 275 monozygotic and 353 dizygotic twin pairs identified through a media campaign in the UK. Snieder and colleagues reported substantial heritabilities for age at menopause, having had a hysterectomy, and age at menarche (panel).

The classic twin study provides the ideal natural experimental situation for assessment of genetic influences on human traits,[2] although large numbers of twin pairs are needed for such studies,[3] especially for those in which data are subject to censoring, as is the case with the menopause. Results from other twin studies will shortly follow. Volunteer twin registries such as the St Thomas' UK adult twin register and that in Australia (panel) provide an invaluable resource for genetic epidemiological research. The implications, which Snieder and colleagues themselves point out, are substantial in terms of primary prevention of and early intervention for diseases related to decreased oestrogen concentrations. Risk of such diseases escalates after the menopause. Although difficulty in measuring similarity of twins' lifelong environments has to be acknowledged, the onset of menopause (or more accurately the permanent cessation of menses) generally in mid-life offers greater opportunity for genetic and environmental factors (even

Twin-pair correlations for age at menopause and related conditions

	UK sample*[1]			Australian samples*		
	MZ(*r*)	DZ(*r*)	h^2† (%)	MZ(*r*)	DZ(*r*)	h^2 (%)
Age at menarche	0·61	0·18	45	0·65	0·18	61–68[7]
Age at menopause	0·58	0·39	63	0·49–0·57	0·31–0·33	31–53†
Hysterectomy	—	—	59	0·61–0·65	0·20–0·32	56–59[6]
Fibroids	—	—	69	0·66	0·34	64†
Menorrhagia	—	—	55	—	—	—
Endometriosis	—	—	—	0·52	0·19	51†

*Intraclass correlations for UK data, polychoric correlations for Australia data except for age at menarche, age at menopause (Pearson product-moment correlations).
†Estimate of heritability. †Unpublished data

age itself) to influence the menopause than a disease or physiological state occurring early in life.

Views of the advantages or otherwise of reproductive senescence differ. Many researchers have sought to explain the end of female reproductive potential on the basis of depletion of ovarian follicles.[4–6] However, ovarian follicles can be depleted by numerous causes, the most drastic being surgical removal. There is evidence that the final "unnatural" curtain on reproductive potential, drawn by surgical intervention in the form of hysterectomy, is also influenced by genes. Snieder and colleagues' findings confirm our report[7] that genetic influences were operating on liability to hysterectomy. Evidence for this process was the much higher concordance between monozygotic twin sisters than between dizygotic twin sisters for hysterectomy (panel). Why should there be such concordance for a surgical procedure? Snieder and colleagues highlighted uterine fibroids and menorrhagia as two of the key reasons for hysterectomy, and showed substantial genetic influences on these disorders. Strong genetic influences on uterine fibroids as a reason for hysterectomy have been found, as have such influences on endometriosis (panel). Genetic covariation requires further exploration. Estimation of genetic correlations between age at natural menopause and postmenopausal cardiovascular disease, osteoporosis, and reproductive cancers is currently possible only when sufficiently large numbers of elderly female twins volunteer for research.

Assessment of the menopause prospectively is the ideal, albeit chronologically convoluted, approach. It is also logistically difficult because only after an interval of 12 months can a woman vouch that a menstrual period was indeed the last, and because women then may no longer see the importance of participating in research on the menopause.[8] In addition, validation and differential diagnosis of vaginal bleeding is a difficulty, since vaginal bleeding may be non-menopausal. To maintain samples of potential study participants prospectively in sufficiently large numbers to provide adequate power is impossible, so researchers commonly have to be satisfied with retrospective data.

The timing of onset of reproductive potential (age at menarche) has been found to be under genetic influence resembling dominance or epistasis (non-allelic interaction),[9] both of which give rise to non-additive effects. Snieder and colleagues found a similar genetic influence in their data, which also raises questions of fitness and selection, because traits that exhibit a large degree of genetic "non-additivity" have repeatedly been shown to have been subject to intense natural selection during evolutionary time. The temptation may be to view age at natural menopause and age at hysterectomy (which may not equate with hormonal menopause) as components of the same phenomenon. Viewing them in this way may obscure their apparently different causal, probably genetic, mechanisms. The same can be said for age at menopause and age at menarche.

Finally, studies by all methods have concluded that age at menopause is closer between monozygotic twins than between dizygotic twins, even after adjustment for confounders that are correlated within families and twinships. Statistical research in this area is both theoretically complicated and computationally intensive. One way to address the problem of treating covariates as fixed effects is to develop multivariate Markov Chain Monte Carlo methods that can incorporate a mixture of censored and non-censored observations.

Traditional biological limitations on fertility, such as the menopause, may well become increasingly irrelevant with new reproductive techniques and with the increasing widespread use of hormone-replacement therapies. Nevertheless, investigation of this important human milestone has important implications for the prevalence of cardiovascular and other diseases such as osteoporosis. Delaying the menopause to postpone these disorders has a more immediate impact than has talk of any future advantage, related to "grandmothering", of a longer postmenopausal life. Hence opportunities for collecting sound uncontam-inated data on the menopause are contracting.

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Prevalence of arthroplasty during the course of rheumatoid arthritis

The development of potent medicines for the treatment of rheumatoid arthritis (RA) has made effective palliation of pain and reduction of disease activity possible for many patients. In addition, the overall severity of the disease seems to be decreasing,[1] possibly because of modern multidisciplinary therapy. Nevertheless, a report by F Wolfe and S H Zwillich[2] provides a timely reminder that RA is still a devastating disease and that progressive destruction continues despite aggressive treatment by experienced rheumatologists.

The modern history of RA care has been punctuated by the discovery and widespread adoption of treatments that yield striking results both in short-term studies and in early clinical experience, but which are disappointing in the long-term maintenance of joint function. This history began with the early use of glucocorticoids, which were initially thought to be potentially curative. Only with time did their therapeutic limitations and adverse metabolic effects become apparent. The dissonance between the encouraging early results and the poor long-term efficacy of RA treatment is due, in part, to the methods of trials in RA. Virtually every controlled study of RA treatment has been limited to less than 24 months,[3] clearly insufficient for a chronic disease. Wolfe and Zwillich have added to the understanding of RA by exploring the natural history of treated RA in a longitudinal study encompassing nearly 25 years and by taking joint replacement as a marker of poor outcome. Their finding of an overall 25% risk of arthroplasty by 22 years after onset of RA in a homogeneous midwestern US population of patients is similar to the 20% rate of large-joint arthroplasty reported for a population of Finnish RA patients.[4] These findings indicate that, although early control of inflammation is important for palliation, it may not arrest progression of joint destruction over a lifetime.

The absence of universally effective therapy for inducing remission in RA has fostered an intensive search for risk factors to permit early identification of patients whose poor prognosis would justify an aggressive approach to treatment. Several factors, such as poor functional indices, high numbers of affected joints, and inflammatory markers, are associated with poorer outcomes in RA.[3,5,6] Wolfe and Zwillich's study also showed that likelihood of arthroplasty, their surrogate marker of joint failure, was related largely to disease severity, and that patients who underwent one arthroplasty were at high risk of repeat surgery. Anaemia, leucocyte count, and absence of smoking history were also identified as somewhat unexpected risk factors.[2]

Although none of the findings was completely surprising, and despite the lack of prognostic power applicable to individual patients, Wolfe and Zwillich have provided a unique glimpse of the natural history of treated RA in a closely monitored group of patients. They were able to do so because of their extensive database and careful follow-up of a large clinical population of RA patients referred to their specialty clinic over the past quarter century; this database alone is a rare resource, especially in the USA, where geographic mobility and medical insurance exigencies typically result in a rapid loss of continuity of care.

The results generated by this analysis, however, must be viewed as merely a baseline. The statistical power was inadequate for the detection of differences in disease progression afforded by the various medicines used to treat RA. Moreover, as pharmacological and multidisciplinary therapeutic approaches to RA have changed, the impact of the newer treatments has not yet been measured. Finally, advances in surgical and anaesthetic techniques, as well as in the durability and functional properties of prostheses, have altered both the risks and the benefits of arthroplasty and have probably affected the overall arthroplasty rate, thereby influencing the surrogate marker without necessarily reflecting changes in disease outcome.

The important perspective reinforced by reports such as Wolfe and Zwillich's is that the natural history of RA spans decades; short-term palliation of inflammatory flares is important and helpful, but ultimately, decisions must be based on long-term prospects. Although the pace of joint destruction is most rapid in the first years of the disease,[3,6] lengthy RA remissions are rare,[7] and the actuarial survival among RA patients remains substantially poorer than normal.[3] The data presented by Wolfe and Zwillich are valuable not because they contribute to the assessment of prognosis for individual patients, but because they present a unique perspective on the natural history of well-treated RA at the end of the 20th century. Documenting true alterations in the natural history of RA may take decades, and it will be years before any of the newer agents can be said to be "disease modifying". Meanwhile, Wolfe and Zwillich have laid a foundation that will permit a comparison of current treatment with a well-described historical standard.

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History and the future

This week *The Lancet* pauses briefly to reflect on 175 years of continuous publication. We are holding a small party in the journal and publishing an accompanying supplement to signal the occasion. You are invited to join us. Guests are always welcome. We hope that you (and we) will be around to participate in the journal's 200th birthday celebrations.

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