components by comparing the similarity within each pair between zygosities. Intraclass correlation coefficients (r) were used as a measure of similarity. One way analysis of variance was used to partition the total variation of osteoarthritis into between pair (B) and within pair (W) variations. The estimate of r is given by the difference between B and W over their sum—that is, $(B-W)/(B+W)$ where the approximate $SE=\sqrt{(1-r)^2(1+r)^2/(n-1)}$ (where r=intraclass correlation, n=number of pairs). A path maximum likelihood (PATH-ML) method was used to estimate the genetic effect. The variances-covariances are expressed as a function of four main effects: additive genetic (A), dominant genetic (D), common environment (C), and specific environment for an individual, including measurement error (E). There was no evidence of a dominant effect and the models tested were, firstly, $y_{ij}=\mu+A_{ij}+C_{ij}+E_{ij}$, secondly, $y_{ij}=\mu+A_{ij}+E_{ij}$, thirdly, $y_{ij}=\mu+C_{ij}+E_{ij}$ (i=family cluster; j=individual within family). There was no significant improvement of the first over the second, suggesting no significant effect of C. The AE model was therefore tested against E to obtain a level of significance with the goodness of fit likelihood ratio statistic.

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Commentary: Genes for osteoarthritis: interpreting twin data

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> "This is indeed a mystery," I remarked. "What do you imagine that it means?"
>
> "I have no data yet. It is a capital mistake to theorize before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts." [1]

Anyone can theorise that genes have a role in determining who gets which diseases and at what stage of life. Anyone can imagine that the world is round not flat. The key element, however, is to show that one's theory is believable by gathering and analysing data, and more data, using designs that ever more critically assess the hypotheses at stake. Columbus was not alone in his anti-flat earth imaginings, but he is famous because he collected critical data (even though he may not have interpreted all of it correctly, given the concept American Indians).

The classic twin method is a clever means of trying to untangle the role of genes from that of shared non-genetic influences on individual characteristics. The similarity of monozygotic (one egg) twin pairs, who are genetically identical, is compared with that of dizygotic (two eggs) twin pairs, who are on average genetically half identical. Given that sampling issues are adequately dealt with,[2] the finding that monozygotic pairs are more similar than dizygotic pairs is consistent with the genetic hypothesis but certainly does not prove it.

If the extent to which twin pairs share the non-genetic influences for that characteristic is truly no greater in monozygotic pairs, however, the genetic hypothesis is substantiated. In applying the classic twin method this is almost always theorised to be the case. The catch, of course, is that it in practice is very difficult to test the veracity of this condition. There is substantial evidence that living together contributes to humans being more similar in lifestyle and psychological, physiological, and other characteristics.[2,3] Dependent on the characteristic in question, this cohabitation effect may abate quickly or slowly as pairs begin to live apart, and may be greater for monozygotic twin pairs.[3-5]

When the classic twin method is applied, therefore, failure to consider zygosity differences in the effects of cohabitation may lead at best to overestimates of and at worst to invalid conclusions about a genetic role.

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Samples of several hundreds of pairs of twins are needed to detect even relatively large effects of cohabitation. Given the usual modelling strategy, finding no such effect when one actually exists will lead to an inflated estimate of the size of the genetic effect.[6] That is, usual application of the method is biased towards finding in favour of a genetic theory and has little power to deal with the alternative non-genetic explanation. If one only wears green glasses, one is bound to conclude that the world is green.

Spector *et al* have applied the method to osteoarthritis. From a sample of twins ascertained by advertisements and other means they found that monozygotic pairs were significantly more concordant for disease at one, possibly two, sites. For a score based on radiographic imaging, about half the variance was attributable to genetic factors under the classic twin method. Note that this does not mean that half of osteoarthritis is due to genes, a naive and incorrect interpretation sometimes made. Attempts were made to allow for non-genetic influences, but given the sample size and statistical power the above figure must be considered to be an upper bound of the genetic "influence."

As the authors indicate, it is now possible to test directly the genetic hypothesis by actually finding the genetic loci implicated and measuring the impact of variation at these putative loci. Replication of such findings is essential as the current controversy over the existence and size of the role of the vitamin D receptor locus on bone density is illustrating.[7,8] Understanding the biological mechanisms of the genes will confirm the truth of the genetic hypothesis and could have considerable clinical importance.

Such gene searches are very expensive and justified only if there is a priori evidence that genetic variation is important for a characteristic. Given the caveats above, the findings of classic twin studies can be informative. Moreover, particular twin pairs are the optimal design for some sib-pair methods of searching for disease genes.[9,10] Hundreds if not thousands of such pairs may be needed to ensure that important loci are not missed, however, and international collaborative efforts may be required. This may be difficult to achieve as there is a danger that the promise of huge commercial gains may overwhelm traditional scientific cooperation.

In summary, genetic research offers new insights into the aetiology, and hopefully the treatment, of diseases. Data from twin pairs will play a pivotal role in this development, but a good deal of circumspection is warranted in interpreting early findings, especially those from studies in which genes are not actually measured. False or inflated claims will be detrimental in the long term.

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Survey of intensive care of severely head injured patients in the United Kingdom

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Abstract

***Objectives*—To study practice in intensive care of patients with severe head injury in neurosurgical referral centres in United Kingdom.**

***Design*—Structured telephone interview of senior nursing staff in intensive care unit of adult neurosurgical referral centre.**

***Setting*—39 intensive care units in hospitals that accepted acute head injuries for specialist neurosurgical management, identified from *Medical Directory* and information from professional bodies.**

***Main outcome measures*—Details of organisation and administration of intensive care and patterns of monitoring and treatment for patients admitted with severe head injury.**

***Results*—Patients were managed in specialist neurosurgical intensive care units in 21 of the centres and in general intensive care units in 18. Their intensive care was coordinated by an anaesthetist in 25 units and by a neurosurgeon in 12. Annual caseload varied between units: 20 received > 100 patients, 12 received 50-100, and seven received 25-49. Monitoring and treatment varied considerably between centres. Invasive arterial pressure monitoring was used routinely in 36 units, but central venous pressure monitoring was routinely used in 24 and intracranial pressure was routinely monitored in only 19. Corticosteroids were used to treat intracranial hypertension in 19 units. Seventeen units routinely aimed for arterial carbon dioxide pressure of 3·3-4·0 kPa, and one unit still used severe hyperventilation to a pressure of < 3·3 kPa.**

***Conclusion*—The intensive care of patients with acute head injuries varied widely between the centres surveyed. Rationalisation of the intensive care of severe head injury with the production of widely accepted guidelines ought to improve the quality of care.**

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Introduction

Half a million patients with head injuries are seen by the health care system in the United Kingdom each year[1]; a fifth of these are admitted to hospital,[2] and 10% of admissions are for severe head injury (defined as a Glasgow coma score of less than 8[3]). Secondary physiological insults contribute to the extent of neurological injury,[4,5] and the quality of intensive care can be a major determinant of outcome. Recent research has re-evaluated some treatment methods that were commonly used in the past.[6,7] However, a recent paper has shown wide variations in the management of severe head injury in the United States, with some centres still using treatments that were not supported