evidence in support of *PRODH* as a susceptibility gene for schizophrenia.

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1 Harrison PJ, Owen MJ. Genes for schizophrenia? Recent findings and their pathophysiological implications. *Lancet* 2003; **361:** 417–19.
2 Liu H, Heath SC, Sobin C, et al. Genetic variation at the 22q11 PRODH2/DGCR6 locus presents an unusual pattern and increases susceptibility to schizophrenia. *Proc Natl Acad Sci USA* 2002; **99:** 3717–22.
3 Jacquet H, Raux G, Thibaut F, et al. PRODH mutations and hyperprolinemia in a subset of schizophrenic patients. *Hum Mol Genet* 2002; **11:** 2243–49.

Sir—Paul Harrison and Michael Owen[1] draw cautious positive conclusions from genetic linkage studies in schizophrenia and point to pathophysiological implications. One can review the same evidence and reach a different conclusion with respect to the genetic basis of psychosis and the direction of future research.

Harrison and Owen cite two meta-analyses[2,3] and claim that "replicated linkages to several chromosomal regions are accumulating". But the striking feature of these meta-analyses is that, despite the fact they include many of the same studies, their summaries agree with respect to only one chromosomal arm (8p) of the nine they highlight. A reasonable conclusion is that the null hypothesis has not been disproved.

Why should this substantial endeavour have revealed so little firm evidence of genetic linkage to psychosis? An alternative to the view adopted by Harrison and Owen (that there are multiple genes of small effect) is that the relevant variation is epigenetic—ie, involves modifications such as methylation of the sequence rather than alterations in the DNA sequence itself. For this reason, the modification is invisible in terms of the linkage strategy.

There are already indications of epigenetic variation in the data from monozygotic twins. Whereas concordance (between 40% and 50%) is greater than that (12–15%) seen in dizygotic twins consistent with a genetic factor, it falls well short of 100%. The discrepancy is often interpreted as evidence for an environmental interaction, but no consistent differences in exposure to putative risk factors between affected and non-affected members of discordant pairs have been identified. The alternative is that discordance reflects a difference in gene expression in the course of development.

These arguments can be placed in relation to the nature of psychotic symptoms—ie, disturbances of human beings' specific capacity for language. Hallucinations (voices), disturbances of thought processes (thoughts experienced as alien, loss of direction), and even delusions (distortions of meaning) can all be conceived as deviations in the transition of thought to speech (production) or from perceived speech to meaning. Thus the phenomena of psychosis are associated with the core characteristic of the species. The importance is that the relevant genetic variation relates to precisely those changes that distinguish *Homo sapiens* from other great ape species.

Already there is evidence from monozygotic twins that asymmetry of the planum temporale and its relation to handedness is subject to epigenetic variation,[4] as is the association between psychosis and asymmetry of the posterior segment of the Sylvian fissure that overlies the planum. Thus, the asymmetry that separates human beings from other species, and the substrate of language, is subject to variation within the species that is independent of the DNA sequence. This epigenetic variation transmitted between generations is dependent on an interaction between maternal and paternal genomes and perhaps stochastic processes in the course of development.

These conclusions lead to future strategies that depart from those of Harrison and Owen. Rather than concentrating resources on ever-widening searches for multiple genes of small effect, they dictate a focus on the characteristics that distinguish the course of brain development in *Homo sapiens* from that in other primates, and on the ill-understood interaction of genetic and epigenetic factors in determining the variation associated with this development.

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1 Harrison PJ, Owen MJ. Genes for schizophrenia? Recent findings and their pathophysiological implications. *Lancet* 2003; **361:** 417–19.
2 Badner JA, Gershon ES. Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. *Mol Psychiatry* 2002; **7:** 405–11.
3 Levinson DF, Lewis CM, Wise LH, et al. Meta-analysis of genome scans for schizophrenia. *Am J Med Genet* 2002; **114:** 700–01 (abstr).
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Authors' reply

Sir—Maria Karayiorgou and Joseph Gogos take us to task for underplaying the evidence that *PRODH* is a schizophrenia susceptibility gene. The format of a Rapid review inevitably means that issues are covered briefly, without being able to do justice to every aspect of the data or their interpretation. Moreover, we were limited to 30 references, and had to remove mention of unpublished data concerning several of the genes. These factors all affected the way we portrayed the background to, and strength of evidence for, each of the genes. It also led us to omit other candidates worthy of mention, such as *DISC1*, *DRD3*, and *HTR2A*.

Nevertheless, Karayiorgou and Gogos correctly point out that their study[1] includes a within-study replication which, to be consistent with the way we summarised the *G72* data, should have been stated in the table. We apologise; the error arose when we simplified an earlier version of the table, which included more details about replications. Although we acknowledge this upgrading of the evidence, we are still cautious about the evidence for *PRODH*, since some comparisons used two-marker haplotypes whereas others used three-marker haplotypes, and the observation was not significant in a third sample (p=0·055, one-tailed)[1] nor in an independent family-based association study.[2] Lack of space and citations also led us to omit the study by Jacquet and colleagues,[3] which certainly provides some additional support for *PRODH* involvement in schizophrenia.

We agree with Tim Crow that epigenetic factors might well be important, and said so in our article. However, we disagree with his negative interpretation of the evidence for any of the loci, and hence for all the genes that we reviewed. The fact that two meta-analyses do not come up with exactly the same result is hardly unexpected, given the emerging methods in this specialty, and variation in the datasets used and approaches adopted. We are more impressed by the similarities than the differences in results between the two meta-analyses, and by the fact that in the larger one,[4] six loci met genome-wide criteria for significance (including 6p and 8p, harbouring *DTNBP1* and *NRG*, respectively). That three of the other five susceptibility genes are also situated at loci with strong, albeit less conclusive, evidence of linkage, surely increases the likelihood that they are true loci for schizophrenia. Moreover, although the evidence might be incomplete with respect to the multiple susceptibility genes model of

schizophrenia, it compares favourably with the lack of empirical data yet available to support Crow's challenging hypothesis.

The two letters show the divergence of opinion that remains about the genetics of schizophrenia. On one hand we are criticised for underestimating the "positive and consistent" evidence for *PRODH*, while on the other we are criticised for proposing the existence of any autosomal genes at all. This state of affairs encourages us to believe that the opinions we expressed lie somewhere close to the middle ground. Ultimately, data will resolve the uncertainty, and determine whether the protocadherin XY is the epigenetic answer to the puzzle.

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1 Liu H, Heath SC, Sobin C, et al. Genetic variation at the 22q11 *PRODH2/DGCR6* locus presents an unusual pattern and increases susceptibility to schizophrenia. *Proc Natl Acad Sci USA* 2002; **99:** 3717–22.
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Granulocyte-macrophage colony-stimulating factor for Crohn's disease

Sir—Brian Dieckgraefe and Joshua Korzenik (Nov 9, p 1478)[1] report on the efficacy of granulocyte-macrophage colony-stimulating factor (GMCSF) for the treatment of Crohn's disease. However, the authors make no reference to our previous publication[2] in which we reported the use of granulocyte colony-stimulating factor (GCSF) to treat Crohn's disease in an adolescent boy whose disease was resistant to other forms of treatment.

Our report clearly outlined the rationale for use of GCSF as reiterated by Dieckgraefe and Korzenik—ie, in the presence of Crohn's-like lesions with conditions of neutrophil dysfunction, including glycogen-storage disease type 1B, chronic granulomatous disease, and congenital neutropenia. We postulated at the time, as do Dieckgraefe and Korzenik, that the benefit of treatment with GCSF could be due to an antibacterial effect with an increase in the number of neutrophils or to an effect on cytokines, including the suppression of tumour necrosis factor α.

Since ours was the first report on the use of colony-stimulating factors in the treatment of Crohn's disease, we were surprised that it was not referenced by Dieckgraefe and Korzenik. Our surprise was accentuated by the fact that the authors had knowledge of our publication; one of us was invited to visit their poster at the American Gastroenterology Association meeting in Atlanta in 2001, which outlined preliminary results of the study published in *The Lancet*. This invitation arose because the authors had been aware of our initial report.

In the conflict of interest statement outlined by Dieckgraefe and Korzenik in their *Lancet* publication, they state that, on the basis of their hypothesis, Washington University has applied for a patent covering the use of "colony-stimulating factors" for the treatment of Crohn's disease. They further state that the technology has been licensed to a commercial firm and that both authors are entitled to royalties. Obtaining a US patent is dependent on being first to invent. In their patent application filed in February, 2000, more than 1 year after our report, Dieckgraefe and Korzenik refer to case reports on the use of colony-stimulating factors to treat Crohn's disease-like lesions associated with defects of neutrophil function. These conditions are not covered by their patent application. By contrast, whereas the first claim outlined in their patent application covers the use of GCSF rather than GMCSF in the treatment of Crohn's disease they do not mention our publication, which remains the only report on the use of GCSF to treat Crohn's disease.

As we stated to Dieckgraefe and Korzenik in Atlanta, we published our report with the intention of stimulating studies such as theirs in the hope that this proposed treatment would be of benefit to patients with intractable Crohn's disease. We did not intend this hypothesis to be subject to patent protection, thereby rendering the treatment less available to many chronically ill patients. Withdrawing their claim for patent protection for GCSF alone, about which they have not published, would be of great benefit to patients if clinical trials confirm the efficacy of colony-stimulating factors in treating Crohn's disease.

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1 Dieckgraefe BK, Korzenik JR. Treatment of active Crohn's disease with recombinant human granulocyte-macrophage colony-stimulating factor. *Lancet* 2002; **360:** 1478–80.
2 Vaughan D, Drumm B. Treatment of fistulas with granulocyte colony-stimulating factor in a patient with Crohn's disease. *N Engl J Med* 1999; **340:** 239–40.

Authors' reply

Sir—Brendan Drumm and David Vaughan are critical of our manuscript for failing to cite their case report,[1] describing GCSF treatment of a rectal fistula. In fact, the first reference we did cite[2] was for a review that summarised evidence supporting an association between Crohn's disease and impaired innate immune function. Drumm and Vaughan's case report was included in this review (reference 36). The format of research letters in *The Lancet* allows for only five references to be included. The limited references we cited were central to reviewers' questions and details of the clinical trial being presented. If we could have cited additional case reports, we would have chosen the seminal observations of Roe and others[3,4] who deserve credit for establishing the gastrointestinal phenotype in glycogen-storage disease type 1B. Finally, Drumm and Vaughan's case report describes the use of an entirely different medication; GCSF has vastly different properties to GMCSF used in our trial. Although both medications increase neutrophil counts, these proteins lack structural similarity, they act on different receptors and cell populations, and they have fundamentally different biological activities.

While we commend Drumm and Vaughan on their observation that GCSF may promote fistula closure, their assertion that our trial was inspired by or followed their work is inaccurate. Our study, examining the safety and effectiveness of GMCSF for the reduction of Crohn's disease activity, was well underway at the time of Drumm and Vaughan's case report.

With respect to the issue raised of inventorship, *The Lancet* has a copy of correspondence and a manuscript submission, documenting our hypothesis and research that greatly predates Drumm and Vaughan's report.

We share Drumm and Vaughan's stated desire that new promising therapies be made widely and rapidly available to patients. However, we believe that the most effective way to accomplish this goal is in the form of well designed clinical trials. Results of such clinical trials and other related investigations are precisely the driving forces that stimulate new avenues of