for example, nasal swabs, ultrasonography, and diagnostic lavage. Others, more suitable for chronic cases, can realistically be undertaken only in a referral centre; these include smears, mucosal biopsy, estimation of the ciliary beat frequency, and sinoscopy. With the possible exception of endoscopy none of these techniques is totally reliable.[4,5] In this issue, van Duijn and colleagues (p 684)[6] have investigated the predictive value of signs and symptoms in the diagnosis of maxillary sinusitis (diagnosed by ultrasonography). General practitioners' clinical diagnoses were confirmed in only half the cases. Even when the diagnosis was weighted by clinical symptoms inaccuracy and uncertainty persisted.

Should this be surprising and, in any case, does it really matter? Recently, with the development of functional endoscopic sinus surgery,[7] some patients with mucosal disease previously thought to be insignificant have been rid of their symptoms. Abnormalities of the lining of the ethmoid sinuses cause mechanical or functional obstruction to drainage of the paranasal sinuses, but under close endoscopic control the ethmoid sinus can be opened through the middle meatus and sufficient tissue removed to allow adequate ventilation and restore mucociliary clearance. Paradoxically, in some clinically successful cases abnormal mucosal changes have persisted; others with endoscopically perfect results have continued to have symptoms. A need clearly exists for more research into the mechanisms of sinusitis and long term clinical trials of treatment.

Unfortunately, general practitioners are in the unenviable position of being the least well equipped to diagnose sinusitis but are being criticised for diagnosing it too often and overprescribing antibiotics. Yet they are liable to litigation should the patient develop complications from infection. Orbital and intracranial sequelae of inadequately treated maxillary sinusitis are still seen regularly today and can have catastrophic consequences such as loss of sight, meningitis, or a brain abscess.

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Transfusing *Yersinia enterocolitica*

Rare but deadly

Severe, often fatal reactions after the transfusion of contaminated blood have been well described.[1] Single unit closed collection systems have greatly reduced environmental contamination of donated blood,[2] but recent cases of infection with pseudomonads have led to renewed calls for strict adherence to aseptic technique in collecting and processing blood and careful temperature control of blood banks.[3] These precautions, however, do not prevent transfusion reactions arising from blood contaminated with *Yersinia enterocolitica*.

Y enterocolitica is a Gram negative coccobacillus that is normally associated with self limiting gastrointestinal illness. Although its optimum temperature for growth is 25°C, it is one of the few human pathogens that can grow at 4°C (incubation at this temperature is used for enrichment culture in the laboratory). Outside the United Kingdom 17 deaths in 27 reported cases of fever and shock immediately after transfusion have been reported with the subsequent isolation of *Y enterocolitica* from the donated unit or the recipient's blood.[4-8] At least six cases with four deaths have occurred in the United Kingdom since the first report in 1988 (R Mitchell, personal communication; J Smillie and F Ala, annual meeting of British Blood Transfusion Society; Nottingham, 3-6 Sept 1991).[9,10] Common features of most reports include the storage of whole blood or red cell concentrates for over three weeks before transfusion and serological evidence of donor infection with *Y enterocolitica* with or without a history of diarrhoea at the time of donation.

Experimental inoculation of small numbers (less than one colony forming unit/ml) of *Y enterocolitica* into units of packed red cells kept at 4°C is followed, after a lag phase of one to two weeks, by exponential growth to over 10^6 colonies/ml after three weeks' incubation, when endotoxin is first detectable.[11] Transfusion reactions are presumed to result from a chain of coincidences in which a mild, even asymptomatic, infection in the donor gives rise to a transient bacteraemia at the time of donation. This seeds the unit of blood with a small inoculum of the organism and, after enrichment culture at 4°C for over three weeks, the unit contains numerous bacteria and associated endotoxin. Transfusing this blood results in septicaemia and endotoxin mediated shock. Although prolonged incubation at refrigerator temperature is usually the rule in reactions, one case has been described after transfusion of platelets (R Mitchell, unpublished communication), which implies rapid growth at 22°C in a medium relatively poor in red cells. To put this problem in perspective, in the United States, which has made most effort to encourage reports of this phenomenon, the Food and Drug Administration is aware of seven deaths in 13 cases since 1986[8] (about one death per nine million transfusions).

Although a rare complication, it has proved difficult to find a simple screening method for blood banks. Conventional serology by agglutination gives numerous cross reactions, may give negative results in acute infection, and may give positive results in 1-4% of some populations. An expert advisory committee of the Food and Drug Administration has summarised other possible approaches and their drawbacks.[8] Excluding donors with a history of gastrointestinal illness in the month before donation would result in unworkable numbers of lost donations and would not detect the asymptomatic donors responsible for most incidents. Conventional culture of all donations is problematic and of uncertain sensitivity. Reducing the time for which whole blood and red cells are stored would have serious implications for the blood supply.

Y enterocolitica does not produce haemolysis of a degree sufficient to render the unit visibly darker when viewed in

isolation, but the colour of the main bag differs from the colour of the segments that remain sterile, presumably because of the tiny initial inoculum per unit volume.[12] Whether this sign will turn out to be useful in screening blood remains to be seen. The Centers for Disease Control in Atlanta have suggested testing each unit over 25 days old for the presence of bacteria before transfusion.[7] This would entail breaching the closed system and conventional culture would result in unacceptable delays. The Food and Drug Administration has not found currently available rapid screening tests for bacteria such as Gram and acridine orange staining and endotoxin assays to be reliable in tests on "spiked" units.[8] A rapid test based on the presence of bacterial 16S ribosomal RNA is currently undergoing trials with encouraging results (K Piper *et al*, 92nd general meeting of American Society for Microbiology, New Orleans, 26-30 May 1992).

In the meantime, it should be emphasised that the reaction to contaminated blood may clinically resemble that to incompatible blood. Standard microbiological investigation with Gram staining and culture of donor blood (or platelets) at 20°C and 37°C is indicated after any severe transfusion reaction with no obvious serological cause. After transfusion has been stopped fever and hypotension should prompt antimicrobial treatment with drugs likely to act against most Gram negative contaminating organisms (for example, iprofloxacin or ceftazidime). Treatment with anti-endotoxin seems logical in cases of strongly suspected or confirmed bacterial contamination of blood or platelet transfusion, although there have been no reports of this application. To enable the delineation of the extent of the problem any suspected cases should be fully investigated and reported to the PHLS Communicable Disease Surveillance Centre, 61 Colindale Avenue, London, or the Communicable Diseases (Scotland) Unit, Ruchill Hospital, Glasgow.

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The molecular genetics of schizophrenia

Blind alleys, acts of faith, and difficult science

Perhaps the greatest set of challenges facing clinical science is to discover the molecular bases of common disorders such as diabetes, coronary heart disease, cancer, Alzheimer's disease, and the functional psychoses. Molecular genetic techniques have been dramatically successful in single gene disorders, which are usually fairly rare. Common familial diseases, however, provide greater problems because of their complex and non-mendelian patterns of transmission.

Nowhere are the difficulties greater than in the study of schizophrenia; here, without objective laboratory tests, we are forced to rely on clinical signs and symptoms, which are often unstable, and on diagnostic schemes, which, though now highly reliable, have no proved validity.[1] Nevertheless, the evidence from family, twin, and adoption studies for an important genetic component is compelling[2] and has persuaded many researchers that the time has come to tackle the aetiology of schizophrenia at a molecular level.

The strategies being adopted can be conveniently divided into two—the "positional cloning" and the "candidate gene" approaches. Positional cloning describes a set of techniques by which disease genes are identified through their position in the genome rather than through their function.[3] In its initial stages the approach relies on linkage analysis, which seeks to find cosegregation of genetic markers with the disease in question in multiply affected families. Clues about where to begin in the search for linked markers may be provided by cytogenetic abnormalities.

For example, the finding of an apparent relation between partial trisomy of the long arm of chromosome 5 and schizophrenia in a Canadian-Chinese family[4] followed by a report of linkage between schizophrenia and DNA markers in the 5q11-q13 region[5] seemed to provide a breakthrough. Unfortunately, other studies did not confirm the linkage, and the disagreements could not be explained by genetic heterogeneity (that is, one form of schizophrenia linked to chromosome 5q and others unlinked).[6]

More recently, several families have been reported in which there is apparent cosegregation of psychotic illness and balanced translocations involving the long arm of chromosome 11.[7-9] Linkage with markers in the relevant region of chromosome 11 has, however, been excluded in a large, combined sample of families multiply affected by schizophrenia from England, south Wales, and Japan.[10]

Yet another possible clue for the location of a locus for susceptibility to schizophrenia comes from the observation that pairs of siblings both affected by schizophrenia are more often than not of the same sex. This might suggest a gene for schizophrenia in the pseudoautosomal region of the sex chromosomes.[11] Two studies have suggested linkage between schizophrenia and a telomeric pseudoautosomal DNA marker,[12,13] but a third study that used the same marker (DXYS14) was resoundingly negative,[14] and the pseudoautosomal hypothesis has also been criticised on statistical grounds.[15]

If, as seems possible, all of the currently available potential shortcuts to finding markers linked to a susceptibility to