outsiders—a formulation of words which unfortunately left open the possibility, as was pointed out by Hadas Ziv of Physicians for Human Rights,[8] that Israel might depart from a universal code of medical ethics in favour of more partisan practices supporting its government. Blachar has, it must be emphasised, time and again put his full weight behind the Israel Medical Association's opposition to torture. Although it is impossible to understand the reality of living in a community that endures random acts of violence, such as that which so brutally took the lives of Applebaum and his daughter, these awkward exchanges within and beyond Israel fill out a welcome space for dialogue—an absolutely necessary prerequisite for peace.

The inclusion of Israel in international organisations, such as the World Medical Association, should not, despite the recent suggestion of psychiatrist and human-rights campaigner Derek Summerfield,[9] be an occasion to provoke withdrawal of national medical associations in protest. Instead, participation in international groupings provides fresh opportunities for concerned outsiders to assist the progress of member nations towards universally agreed standards of practice and behaviour. By publishing Summerfield's criticisms of both the Israel and World Medical Associations, the *BMJ* has been accused of demeaning itself and "promoting hatred and misunderstanding".[10] Yet Summerfield's article has enabled others to reply to and refute his arguments, and to set out their views about the region's predicament. The total effect of these exchanges[5–10] is to take us a small step closer to replacing violence with reason.

To somebody living outside the Middle East, the Israeli-Palestinian conflict seems little more than a perpetual cycle of vengeance. Yet politicians, led by the US government, are working hard towards the creation of a safe and secure permanent Palestinian state by 2005. To move from a policy of vengeance to one of peace, from an essentially military to a political strategy, will require so far undiscovered reserves of trust and confidence among all negotiating parties. Doctors are not, first and foremost, politicians. They are not full-time UN ambassadors, international lawyers, or human-rights activists. But as doctors, their values—creating sustainable partnerships, instilling hope, restoring dignity, and rendering compassion—are vital elements not only of effective clinical practice, but also of building long-lasting peace. Indeed, it is these same values—expressed in society's institutions, work, and public debates—that are the targets of violence, destroying, as the violent intend to do, all that is human about human beings. These values, which underpin every successful episode of healing, are the very fabric of the cloth needed to cradle peace in the Middle East. Recalling these values, reaffirming their truth, and acting on them free from ideology would be honourable tributes to the life and work of David Applebaum—steps towards dismantling an ever more elaborate architecture of hate and humiliation.

An obituary of Dr David Applebaum will appear in next week's issue.

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Conformational exposure: a new handle on prions

Prion diseases, such as Creutzfeldt-Jakob disease, are fatal, incurable, and hard to diagnose. Fear about the link between variant Creutzfeldt-Jakob disease and bovine spongiform encephalopathy continues to fire public concern, especially with the recent identification of a cow with bovine spongiform encephalopathy in Canada.[1] As bovine spongiform encephalopathy becomes a worldwide problem, many researchers seek novel ways to improve diagnosis and possibly open avenues to future treatments for these neurodegenerative conditions. Definitive diagnosis of these diseases depends on postmortem verification of the deposition of protease-resistant prion protein (PrP^{Sc}) in central nervous tissue of patients. Hallmarks of the pathology of the diseases are also seen: gliosis, vacuolation, and loss of neurons.[2]

Whilst neurological changes give good probable diagnosis, it would be much better to be able to know for certain that a patient has Creutzfeldt-Jakob disease before death or, even more ideally, before symptoms progress to the point where the patient has irreversible dementia. Research has largely focused on identification of surrogate markers or more sensitive ways of detecting PrP^{Sc}. The protein 14-3-3 is often used but testing for this protein requires cerebrospinal fluid.[3] For a while it was hoped[4] that a cyclic form of protein amplification to detect PrP^{Sc} would allow the marker to be detected in blood, but this advance has not occurred. Specific detection of PrP^{Sc} requires removal from brain sections or extracts of its normal isoform, PrP^{c}, which is expressed in the brains of all mammals. Attempts to develop an antibody specific for the abnormal form have been largely unsuccessful and the antibodies used in commercial assays, such as the one developed by Prionics,[5] have been notoriously difficult to use.

Therefore the recent report by Eustache Paramithiotis and colleagues[6] of a method to generate highly specific antibodies that recognise PrP^{Sc} is a breath of fresh air in the prion field. These investigators developed several antibodies that are specific for PrP^{Sc}. They searched for epitopes that become exposed when the prion protein becomes misfolded, and identified three aminoacid residues that occur twice in the protein. Arg-Arg-Tyr (YYR) is the motif and peptides based on this motif were used to immunise rabbits and generate a polyclonal antibody that identified PrP^{Sc} in vitro in different species with prion disease, including sheep, cows, and man. Paramithiotis and colleagues also developed a series of other antibodies that selectively identify PrP^{Sc}. Thus this novel conformational exposure of a small part of the prion protein allows selective identification of its rogue conformer.

As well as detecting PrP^{Sc} in brain tissue the YYR antibody also detected PrP^{Sc} in mouse spleen, opening up the possibility that this antibody might allow diagnosis before death. This antibody might also improve detection of PrP^{Sc} in tonsil biopsy specimens, which has been

proposed as a possible preclinical test.[7] The use of this antibody in an effective preclinical test for prion disease would make the identification of this conformationally exposed epitope an important breakthrough. However, close examination of several blots in Paramithiotis and colleagues' report suggests that protease-sensitive PrP is also bound by the antibody. The investigators suggest that this protein is misfolded but protease-sensitive PrP. However, some of this material could be PrP^{c}, the normal isoform.

The selectivity of these antibodies will require confirmation by independent groups before its use clinically for selective diagnosis can be confirmed. Also, why such a small epitope, YYR, which occurs in many proteins, would not bind these antibodies in a range of proteins is mysterious. The advantage of these antibodies would be the elimination of the time-consuming digestion-step of proteinase K that is commonly used. This digestion probably destroys 90% of other proteins in a brain extract or section, thus leaving PrP^{Sc} the major resistant protein. If this step cannot be eliminated, this antibody would not be much of an advance on current techniques.

Since the finding that applying PrP antibodies to cell cultures results in the elimination of PrP^{Sc} from infected cells,[8] the use of prophylactic treatment of patients by the use of immunisation or delivery of antibodies against PrP has been a real possibility. First success came in mouse experiments.[9] Immunisation of mice with recombinant PrP extended the incubation period. Further work also suggests that mice transgenically expressing antibodies against PrP would be protected against the disease,[10] and that injection of antibodies directly into mice also inhibits onset of prion disease.[11] The implication is that a very specific antibody, like those against the YYR epitope, would be a possible effective treatment for prion disease. However, there is one problem with this concept. To apply such a treatment in human beings, Creutzfeldt-Jakob disease must first be positively identified. Therefore, although using antibodies as a treatment has given optimistic results and the use of a logical method (as used by Paramithiotis and colleagues) for generating PrP^{Sc}-specific antibodies should be applauded, the cart remains before the horse until someone develops a fool-proof rapid diagnostic test for prion disease that is effective either for presymptomatic or early symptomatic cases of Creutzfeldt-Jakob disease. Such tests are currently only remote possibilities.

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Mendelian randomisation: a new spin or real progress?

A recent statement that "In the genetics of complex diseases, association is in danger of becoming a rather dirty word"[1] calls to mind that similar sentiments were expressed nearly 30 years ago after a series of studies were published on the associations between various diseases and blood groups and HLA variants.[2] During this period, the human genome project has been completed, and new technologies for genomic analysis have been developed. Epidemiological methods and understanding of the biases of human observational studies have also advanced.

Genetic association studies are undergoing a renaissance under the banner of Mendelian randomisation. George Davey Smith and Shah Ebrahim[3] recently suggested that studies of the association between diseases and gene variants of known function may share with randomised controlled trials the advantage of excluding confounding as an explanation for a relation. Thus, in a population-based study of a genotype-disease association, the random assortment of alleles at the time of gamete formation (Mendel's second law) results in a random association between loci in a population and is independent from environmental factors. In theory, this random assortment brings about a similar distribution of variants at unlinked genetic loci between individuals with and without disease. This situation is analogous to adequately sized randomised controlled trials in which the random assignment to the intervention or control results in similar distributions of confounders (both measured and unmeasured) between the trial groups. The second step to Davey Smith and Ebrahim's reasoning is that for genes known to modulate the effects of environmental exposure, genetic variants with known functional effects can be considered as markers of altered exposure to an environmental factor of putative causal importance. Therefore the investigation of gene-disease associations potentially enables the effect of environmental exposures to be determined, excluding confounding as an explanation for the association.

Although these developments provide an exciting promise for epidemiological studies of gene-disease associations in the Human Genome Project era, there are some caveats. First, size matters. By contrast with the theoretical promise of Mendelian randomisation, the non-replication of association studies is well known.[4] Davey Smith and Ebrahim note that the major factor accounting for non-replication of results is likely to be inadequate statistical power, coupled with publication bias. This issue is analogous to the experience with randomised controlled trials, where evidence from small trials has not been confirmed in subsequent larger trials.[5] Publication bias is one explanation, but the distribution of confounders may also have differed between groups in smaller trials. As with trials, more consistent associations will be likely to be observed as the investigation of gene-disease associations matures—ie, moves from small innovative studies to large well-designed studies in which potential biases are kept to a minimum. In a recent meta-analysis, an excess of studies replicated the initial report, which likely was not due to publication bias.[6] The scientific record needs to be as