Saturday 7 March 1998

BMJ

MMR vaccination and autism 1998

Déjà vu—pertussis and brain damage 1974?

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The media excitement and public concern after a *Lancet* report linking measles, mumps, and rubella (MMR) vaccine with autism[1] kindles a sense of déjà vu. It is highly reminiscent of similar scares over pertussis in the 1970s,[2] which resulted in much suffering and many deaths from pertussis both in Britain and internationally.[2 3]

Britain's vaccination programme has hugely reduced the incidence of diphtheria, haemophilus meningitis, measles, polio, pertussis, congenital rubella, and tetanus.[4] As the incidence of these diseases has fallen vaccine safety has assumed greater importance, especially in parents' minds. Any safety issue requires cool scientific consideration.[3] Here the hypothesis is that MMR leads to a non-specific gut condition permitting the absorption of non-permeable peptides, which in turn cause serious developmental disorders.[1] Supportive evidence consists of cases referred to a gastroenterology group. The data published comprises 11 boys and one girl, each with bowel abnormalities and serious developmental regression (nine had autism). In eight children parents reported regression starting shortly after the children received MMR.[1]

An editorial accompanying the article and a recent review by the World Health Organisation list the considerable evidence against this and previous related theories from the same group.[3 5] Since each year over 600 000 British children receive MMR in their second year, an age when autism can typically manifest itself, chance alone dictates that some cases will appear shortly after vaccination.[3] Cases will be selectively referred to a group known for its interest in MMR, inflammatory bowel disease, and autism, so the hypothesis rests on clinical anecdote rather than an epidemiologically sound base.

Proved serious vaccine reactions are characterised by specific clinical or laboratory findings, but the non-specific nature of the developmental and gut abnormalities in these cases is striking, and no precise case definition is offered.[1] No vaccine viruses were reported in the children's biological specimens, though the researchers have previously reported viruses in bowel tissues of children with inflammatory bowel disease, findings which others have been unable to confirm.[3]

Epidemiological evidence is unsupportive: the WHO found no links between measles, MMR, and inflammatory bowel disease[5]; and a survey of conditions associated with autism did not mention inflammatory bowel disease.[6] National data seem to indicate a rise in the incidence of autism, but it started over a decade before MMR's introduction in 1988 and showed no change at that time (M Bax, D Lawton, Family Fund Trust, unpublished data). This evidence suggests either no causative association or one that is exceedingly rare. These and many other data relating to MMR safety have been reviewed by the Joint Committee on Vaccination and Immunisation, which found no case for changing vaccination policy. Unproved theories are no basis for dropping a vaccine of proved global safety and effectiveness.[3 5]

Despite the lack of evidence of a causal relation, and the experience of other hypotheses from the same group (linking first wild measles, then measles vaccine, and latterly MMR with bowel disease) not standing up to independent scrutiny[5 7] much parental anxiety has resulted. MMR immunisation rates have begun to decline and those at the "sharp end" of immunisation—general practitioners, health visitors, and community paediatricians—are experiencing parental inquiries.[8] Any decline in immunisation, or the giving of MMR as three injections at annual intervals (as suggested by one of the report's authors), will undo the recent near elimination of measles and rubella in the UK.[8]

The experience with pertussis in the 1970s was also based on anecdotal case reports linking pertussis vaccination with infant brain damage.[9] Again a temporal link between a vaccine and a devastating childhood condition whose natural peak onset was at the very time when most children received that vaccine was misinterpreted as a causal relation. A national study eventually showed that, while there was a temporal association with encephalopathy, any risk of lasting damage was so rare as to be unquantifiable.[10] But the initial report, then as now, attracted media attention; parental and professional anxiety soared; and national immunisation rates fell from 80% to 30%. The number of susceptible children rose, and in the 12 years after 1976 three major pertussis epidemics accounted nationally for over 300 000 notifications and at least 70 deaths. The suffering of families experiencing long miserable illnesses was considerable, and in some cases long term damage ensued. Some parents came to believe that an immunisation they had approved had damaged their child.

There are differences between then and now. The connection of encephalopathy with pertussis vaccine was biologically more plausible than the link proposed for MMR and autism. The original national study[10] has already shown no link between measles vaccine and long term developmental disorders.[11] Detection of vac-

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cine reactions is more efficient, with international data sharing and a careful eye on safety by independent scientific experts on the Joint Committee on Vaccination and Immunisation and committees of the Medicines Control Agency. Surveillance results in product withdrawal when there is clear evidence of a safety issue.

In the 1970s immunisation had a low priority, and evidence based information for those doing the immunising was minimal. District immunisation coordinators did not exist, and vaccination rates slumped partially because it was unclear whose responsibility it was to do anything about them.[12] The pertussis experience must not be repeated with MMR vaccine. While no vaccine can be guaranteed to be without any risk, this has to be weighed against the huge advantages of protection against disease. Seeds of concern have been sown among parents and no doubt will continue to be spread. Those advising families must make sure parents can base their decisions on hard science and evidence.

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1 Wakefield AJ, Murch SH, Linnell AAJ, Casson DM, Malik M, Berelowitz M, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis and pervasive developmental disorder in children. *Lancet* 1998;351:637-41.
2 Gangarosa EJ, Galazka AM, Wolfe CR, Phillips LM, Gangarosa RE, Miller E, et al. Impact of the anti-vaccine movements on pertussis control: the untold story. *Lancet* 1998;351:356-61.
3 Chen RT, Destefano F. Vaccine adverse events: causal or coincidental? *Lancet* 1998;351:611-2.
4 Salisbury DM, Begg NT, eds. *Immunisation against infectious disease.* London: HMSO, 1996.
5 World Health Organisation. Expanded programme on immunization (EPI)—association between measles infection and the occurrence of chronic inflammatory bowel disease. *Wkly Epidemiol Rec* 1998;73:33-40.
6 Fombomme E, Du Mazaubrun C, Cans C, Grandjean H. Autism and associated medical disorders in a French epidemiological survey. *Am Acad Child Adolesc Psychiatry* 1997;36:1561-9.
7 Metcalfe J. Is measles infection associated with Crohn's disease? *BMJ* 1998;316:166.
8 Begg N, Ramsay M, White J, Bozoky Z. Media dents confidence in MMR vaccine. *BMJ* 1998;316:561.
9 Kulenkampff M, Schwartzman JS, Wilson J. Neurological complications of pertussis inoculation. *Arch Dis Child* 1974;49:46-9.
10 Miller D, Madge N, Diamond J, Wadsworth J, Ross E. Pertussis immunisation and serious acute neurological illnesses in children. *BMJ* 1993;307:1171-6.
11 Miller D, Wadsworth J, Diamond J, Ross E. Measles vaccination and neurological events. *Lancet* 1997;349:730-1.
12 Nicoll A, Elliman D, Begg NT. Immunisation: causes of failure and strategies and tactics for success. *BMJ* 1989;299:808-12.

Hydroxychloroquine retinopathy: is screening necessary?

Intensive screening is not necessary at normal doses

The 4-aminoquinolines (chloroquine and hydroxychloroquine) are used as second line agents for their disease modifying effect in rheumatoid arthritis and systemic lupus erythematosus. The association between chloroquine therapy and pigmentary maculopathy has been known since 1959.[1] The manufacturer's datasheet suggests that all patients receiving hydroxychloroquine should undergo an ophthalmic examination, including a central visual field test, at least twice a year. If implemented this recommendation would have a noticeable impact on the ophthalmic service. Is it necessary?

The earliest sign of chloroquine retinopathy is a paracentral scotoma. This so called premaculopathy can be detected with an Amsler chart.[2] Later, subtle pigmentary mottling develops at the macula, and this may progress to the characteristic bull's eye maculopathy and widespread retinal pigment epithelial atrophy. In its early stages chloroquine retinopathy is reversible by stopping the drug.[3] Hydroxychloroquine given at currently prescribed doses is thought to be less toxic than chloroquine.

The recommended dose for hydroxychloroquine is 6.5 mg/kg lean body weight per day.[4] In their prospective study of 73 patients treated with hydroxychloroquine for at least 18 months, Morsman et al reported one case of possible toxic retinopathy—and this patient had received twice the recommended daily dose.[5] In a retrospective study of 82 patients taking hydroxychloroquine for over a year (mean 38.6 months) Spalton et al found no cases of retinopathy.[6] No correlation was present between the computerised visual field indices and any measure of increasing drug exposure. The authors concluded that visual field testing was unnecessary in these patients.[6] Bernstein analysed all published cases and Food and Drug Administration reports of hydroxychloroquine retinopathy. He found no evidence of permanent visual loss among more than 1500 patients who did not exceed the recommended daily dosage for up to 10 years.[7] More recently, however, two well documented cases of hydroxychloroquine retinopathy have been reported in patients treated for 6.5 and 8 years without exceeding the recommended maximum daily dose.[8]

The Royal College of Ophthalmologists' guidelines for managing patients receiving hydroxychloroquine recommend a baseline ophthalmic examination at the start of treatment, including best corrected visual acuity, fundoscopy, and a central visual field test.[9] Thereafter the prescribing medical practitioner should be responsible for any screening considered necessary. Patients should be warned to report any visual disturbance and may be given an Amsler chart to use on a monthly basis. No further ophthalmic examination is necessary unless the patient becomes symptomatic.

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Current evidence suggests that hydroxychloroquine retinopathy is extremely rare if the recommended dose is not exceeded. In most cases a baseline ophthalmic assessment and issue of an Amsler chart with instructions on its use will suffice. The small number of patients who have received hydroxychloroquine for longer than six years should be kept under ophthalmic review until more information is available about the safety of long term treatment.

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1 Hobbs HE, Sorsby A, Freedman A. Retinopathy following chloroquine therapy. *Lancet* 1959;ii:478-80.
2 Easterbrook M. The sensitivity of Amsler grid testing in early chloroquine retinopathy. *Trans Ophthalmol Soc UK* 1985;104:204-7.
3 Crews SJ. Chloroquine retinopathy with recovery in early stages. *Lancet* 1964;ii:436-8.
4 Mackenzie AH. Dose refinements in long-term therapy of rheumatoid arthritis with antimalarials. *Am J Med* 1983;75(suppl):40-5.
5 Morsman CDG, Livesey SJ, Richards IM, Jessop JD, Mills PV. Screening for hydroxychloroquine retinal toxicity: is it necessary? *Eye* 1990;4:572-6.
6 Spalton DJ, Roe GMV, Hughes GRV. Hydroxychloroquine, dosage parameters and retinopathy. *Lupus* 1993;2:355-8.
7 Bernstein HN. Ocular safety of hydroxychloroquine. *Ann Ophthalmol* 1991;23:292-6.
8 Mavrikakis M, Papazoglou S, Sfikakis PP, Vaiopoulos G, Rougas K. Retinal toxicity in long term hydroxychloroquine treatment. *Ann Rheum Dis* 1996;55:187-9.
9 Royal College of Ophthalmologists. *Chloroquine, hydroxychloroquine and the eye*. London: RCO, 1993.

Blood transfusion risk: protecting against the unknown

Worries over variant CJD should not detract from work on other, better known, risks

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In relation to viruses—which, classically, have posed the greatest potential risk to transfusion recipients—British blood is among the safest in the world. For HIV, the risk per unit of transfusion is about 1 in 2.5 million.[1] But British blood services are now faced with the challenge of managing a potential risk from the transmissible spongiform encephalopathies, notably variant Creutzfeldt-Jakob disease. This challenge is particularly difficult given the lack of firm data on either the likely scale of variant Creutzfeldt-Jakob disease infection in Britain or the likelihood that the causative agent is present in and transmissible by donated blood. The announcement by the Department of Health, following advice from the Committee on Safety of Medicines, on 26 February of "further precautionary measures" in relation to the use of British plasma in blood products brings the challenge sharply into focus.

In March 1997 the World Health Organisation concluded that there is no proved or even probable instance of transmission of Creutzfeldt-Jakob disease by blood, blood components, or plasma derivatives, though it did identify a requirement to assess further the potential risk posed to transfusion by variant Creutzfeldt-Jakob disease.[2] Lack of evidence of risk is not evidence of absence of risk.[3] The report that PrP deposition can be identified in tonsillar biopsy specimens from patients with variant Creutzfeldt-Jakob disease suggests greater lymphoreticular involvement than that seen in classical forms of the disease.[4] In response to these and other data the Department of Health, following the advice of the Spongiform Encephalopathy Advisory Committee, commissioned an independent risk assessment of the possibility that leucodepletion of blood components might reduce any risk of transmission of variant Creutzfeldt-Jakob disease by transfusion. The outcome of this is still awaited. This, taken in conjunction with the Committee on Safety of Medicines' recommendations, is likely to result in fundamental changes to the provision of transfusion services and products in Britain.

The Committee on Safety of Medicines has identified several measures which together aim at both ensuring the continued availability of safe and effective plasma products and minimising the risk of exposure to variant Creutzfeldt-Jakob disease through these products. Measures include a requirement to recall products manufactured from plasma pools that include donations from individuals *strongly suspected* of suffering from variant Creutzfeldt-Jakob disease, thus extending previous recommendations that covered only confirmed cases. To minimise the impact of any future recalls albumin made from British plasma will no longer be used as an excipient in medicinal products, including vaccines. Recombinant factor VIII (presumably incorporating a "safe" source of human albumin stabiliser) will be made available for all new patients with haemophilia and for those aged under 16.

All medicinal products manufactured from British donor plasma will be reviewed to determine which products should in future be produced from plasma sourced from countries which do not have clusters of cases of variant Creutzfeldt-Jakob disease. The plasma fractionation centres in England and Scotland will be allowed to import plasma for onward manufacture. The Medicines Control Agency will inspect the suppliers of this plasma to determine that their source donors, even if paid, are as safe as British donors in respect of viral transmission. British transfusion specialists have long promoted voluntary unpaid donation as a mechanism for assuring the safety of blood components and products. In attempting to reduce the theoretical risk of transmitting variant Creutzfeldt-Jakob disease we need to ensure that other infectious risks are not forgotten.

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The safety of fractionated products has improved greatly in recent years and is assured by a number of approaches. Meticulous donor selection procedures, careful inventory management, and testing with the polymerase chain reaction may enable plasma pools to be created from paid donors with viral loads similar to those present in pools derived from unpaid volunteers (J Reilly, data presented at conference on blood safety, Washington, 1998). When combined with specific steps in the manufacturing process to inactivate and remove viruses, such approaches will assure the safety of products in relation to viral transmission. This may not be possible for all products, and the Committee on Safety of Medicines may conclude that in some instances British plasma remains the preferred source. Anti-D immunoglobulin may fall into this category. In such cases clinical indications will need to be re-evaluated—including, for anti-D, the recent recommendations on antenatal prophylaxis.[5]

With access to alternative supplies of plasma the British fractionation centres will be able to continue production, ensuring that their facilities, expertise, and trained staff are not lost. Investment in research in this area will be needed to aid understanding of the distribution of variant Creutzfeldt-Jakob disease in blood and possible methods to remove or inactivate the agent. Hopefully in time it will be possible to resume processing of British plasma.

How will this be judged? New cases of variant Creutzfeldt-Jakob disease in the population are meticulously monitored, and epidemiologists will refine models to predict the likely size of any epidemic and when it may peak following the removal of infected beef from the food chain. Understandably, huge interest has been generated by the report of a monoclonal antibody that can discriminate between normal and abnormal prion protein.[6] It is hoped that this may lead to a test to detect infected individuals and to possibilities for affinity purification of plasma products to remove any abnormal prion protein.

This comprehensive package of precautionary measures has obvious resource implications. Just as these precautions should be seen in the light of the bovine spongiform encephalopathy epidemic, so, we hope, will the identification of resources. With reorganised blood services striving to improve consistency and good practice while finding efficiency savings, new policies should not detract from other areas of blood safety. We have a difficult message to convey to blood recipients and to blood donors: British blood is safe, but we are always seeking ways of making it safer. One of our first challenges following these announcements is to persuade donors that they are still urgently needed and that, as always when we have needed them, they should continue coming forward to give their blood.

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1 Williamson LM, Heptonstall J, Soldan K. A shot in the arm for safer blood transfusion. *BMJ* 1996;313;1221-2.
2 *Report of a WHO consultation on medicinal and other products in relation to human and animal transmissible spongiform encephalopathies*. Geneva: WHO, 1997 (WHO/EMC/ZOO/97.3).
3 Ricketts MN. Is Creutzfeldt-Jacob disease transmitted by blood? Is the absence of evidence of risk evidence of absence of risk? *Can Med Assoc J* 1997;157:1367-70.
4 Hill AF, Zeidler M, Ironside J, Collinge J. Diagnosis of new variant Creutzfeldt-Jacob disease by tonsil biopsy. *Lancet* 1997;349:99-100.
5 Royal College of Physicians of Edinburgh/Royal College of Obstetricians and Gynaecologists. Consensus conference April 1997. *Transfusion Medicine* 1997;7:143-4.
6 Korth C, Stierli B, Streit P, Moser M, Schaller O, Fischer R, et al. Prion (PrP^{sc})-specific epitope defined by a monoclonal antibody. *Nature* 1997:390:74-7.

Patient data, confidentiality, and electronics

Identifiable data should no longer be freely available within the NHS

"Banks access computer records, foreclose on cancer patients."[1] This emotive headline from America in 1993 demonstrated the risks to confidentiality posed by electronic patient records—which are easy to inspect, copy, and transmit without anyone knowing. In Britain, attempts by the medical profession to ensure that such headlines should never be seen here led to fundamental disagreements with the Department of Health. These in turn stalled the already slow development of electronic data handling in the NHS. Only now, with the publication in December of the Caldicott report, is a way forward beginning to emerge.

Shortly after this American headline, the BMA and the Department of Health first discussed confidentiality within the NHS information strategy. The Department of Health (and the NHS Executive) believed all electronically held clinical data should be shared through "the wider NHS family" to facilitate NHS management,[2] but the wider family turned out to be almost anyone in contract with or relating to the NHS, whether clinically involved or not. The BMA felt that patient confidentiality would be so threatened that the only ethical solution was to keep all identifiable clinical data within the clinical domain.[3]

After failing to reach any agreement for several years, the two sides last year agreed to the setting up of a review of the problem of identifiable patient information within NHS information systems under the chairmanship of Dame Fiona Caldicott.[4] The aim was to study flows of identifiable patient data in NHS business to decide whether the inclusion of identifiers was justified and what action could be taken to minimise potential breaches of confidentiality.

Given that the NHS Executive believes that authorised insiders misusing their position represent the most serious threat to confidentiality, it was particularly appropriate that the executive should undertake this

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review. As an NHS Executive review studying NHS procedures in the light of rules set down by the executive,[2] it is no surprise that all the business flows studied, such as general practitioners' family planning claims and extracontractual referrals, were deemed justified in containing patient identifiers. Nevertheless, the report went on to develop principles of confidentiality and build recommendations on these principles about how the NHS should handle electronically held patient data. These are to apply across the administrative and clinical arms of the NHS and are the start of a continuing process.

The better parts of the report state good practice for NHS electronic health records for the first time; the bad bits will require further negotiation to bring the recommendations back in line with the principles. A particular problem is the idea that the NHS number will act as a "de-identifying" variable in patient data (thereby supposedly enhancing protection of the data). In a computerised NHS, however, the NHS number is actually a better identifier than the patient's name and address. To solve this problem, pilot studies are under way to look at controlling access to the NHS number, and hence clinical records, in active NHS use. Nevertheless, and despite these real problems, the most valuable feature of the report is its promotion of a culture change within the NHS administrative machine. The report insists (and in accepting the report the NHS Executive has accepted) that identified data are longer freely available for all to see within the NHS.

What does this mean for clinicians? Work—and thought. It is no longer enough to say that data privacy is somebody else's problem, because clinicians are ultimately responsible for the safety of the patient data they commit to electronic transfer or storage.[5] This responsibility is wide and poorly understood. In the same way as paper records require proper care, so must clinical computer systems store data safely, and transmit data only to other appropriate safe havens, usually clinical ones. If clinicians cannot ensure that, they must see that the data have their identifiers removed before being committed to electronic media. This concept is new for many clinicians, and, while relatively easy in general practice, is a problem for most hospitals, which have traditionally been relaxed about care of patient data. This concept poses particular questions about research databases and registers, and the data guardians proposed by Caldicott to effect and enforce the report's principles will require considerable support, education, and training for their role (which the NHS Executive has agreed to finance).

Another American newspaper article recounts how a patient made the reasonable request that his electronic data should be identifiable only on the ward computer terminal.[6] This apparently simple request created enormous problems for the hospital computer system because confidentiality had not been designed in from the start. The risk exists that the same thing could happen in Britain if the residue of the internal market makes clinicians and administrators feel justified in breaking patient confidentiality. Given the advice of the BMA,[3] the Caldicott report, and adequate money now delivered for protecting confidentiality, there is no longer any excuse for either the executive or clinicians to fail to protect patient data adequately.

A peripheral issue the Caldicott report brings in its train is whether the NHSnet confers confidentiality, for the two are often confused. The NHSnet is the developing NHS intranet for exchanging business and clinical electronic messages, and many had hoped it would solve the confidentiality problem for patient data. Unfortunately it does not, being only a set of dedicated telephone wires. Safe carriers are helpful but not an answer, for the risk to patient data is not in transit, but at workstations throughout the NHS where the data are used.

The final question for confidentiality is how the NHS Executive will ensure that it gains informed consent from patients to use their data, a task the Caldicott review declined to tackle. The true sign of how seriously confidentiality is regarded by the NHS will be the action the executive takes to make informed consent the gold standard for handling patient identifiable data.

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1 RMs need to safeguard computerised patient records to protect hospitals. *Hospital Risk Management* 1993 Sep:129-40.
2 NHS Executive. *The protection and use of patient information.* Leeds: NHS Executive, 1996.
3 Anderson RJ. *Security in clinical information systems.* London: BMA, 1996.
4 Department of Health. *Report on the review of patient identifiable information.* London: Department of Health, 1997. (Caldicott report.)
5 General Medical Council. *Confidentiality.* London: GMC, 1995.
6 Garfinkel S. Computers compromise privacy, cut cost of care. *Boston Globe* 1997;Jun 5.

Immunosuppressive drugs after lung transplantation

New agents may improve long term survival

Survival figures after lung transplantation for the period up to 1996 were reported at a recent annual meeting of the International Society of Heart and Lung Transplantation in London. Although quality of life for patients is greatly improved for some years after transplantation, five year survival after heart-lung, single lung, or double lung transplantation is still less than 50%.[1] Mortality in the first 30 days has improved because of advances in surgical technique and in methods of lung preservation,[1] but after 30 days the survival curves in 1988-91 and in 1992-5 are parallel.

The main cause of death between 30 days and a year after transplantation is infection. After a year the main cause is bronchiolitis obliterans syndrome. This

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fibroproliferative disorder affects the small airways of at least half of patients who survive for three months after transplantation.[2] Its pathogenesis is unclear but it represents a fibrotic repair process occurring after chronic airway injury, and retrospective series have shown that acute lung rejection is an important risk factor for its development.[2] New treatments for bronchiolitis obliterans syndrome and steroid resistant rejection have included trials of inhaled cyclosporin, total lymphoid irradiation, and methotrexate.[3-5] However, since infection is still an important cause of death after lung transplantation,[6] further gains in survival will be difficult to achieve with current immunosuppressive regimens: cyclosporin, azathioprine, steroids, and cytolytic drugs. More effective immunosuppressive drugs are needed, and clinical trials evaluating new immnuosuppressive agents in lung transplantation are planned. Currently, encouraging results have been reported with these drugs after renal transplantation.

Better absorption of a new formulation of cyclosporin—cyclosporin microemulsion formulation (Neoral, Novartis)—increases overall exposure of patient and graft to cyclosporin without an increase in toxicity. The improved pharmacokinetic profile has been shown in healthy human volunteers and stable renal and lung transplant patients, including patients with cystic fibrosis.[7]

Tacrolimus is the United States approved name for FK506 (Prograf, Fujisawa). Gjertson et al examined data from the United Network for Organ Sharing kidney transplant registry on 38 057 patients who had been discharged after their first cadaveric kidney transplant.[8] They compared kidney half life in different treatment groups and found it was 13.8 years for patients taking tacrolimus, 8.8 years for patients taking cyclosporin, and 7.7 years for patients taking other drugs. The authors stated that FK506 seemed to be the first drug significantly to improve long term survival of kidney grafts.

In the only properly controlled study comparing cyclosporin and tacrolimus treatments in lung transplantation there was a trend towards improved survival at two years in the tacrolimus group and a reduction in rejection episodes (0.85/100 patient days for tacrolimus and 1.09/100 patient days for cyclosporin; $p = 0.07$).[9] Notably, however, fewer patients in the tacrolimus group developed obliterative bronchiolitis compared with the cyclosporin group (21.7% *v* 35.8%, $P = 0.025$). Tacrolimus may be effective in treating persistent rejection and in slowing down deterioration in airflow that occurs with bronchiolitis obliterans syndrome.[10]

Mycophenolate mofetil (Cellsept, Hoffmann LaRoche) is a morpholinoethyl ester of mycophenolic acid and has been more extensively studied in controlled, open, and blinded clinical trials than any other new immunosuppressant. In all studies mycophenolate has been substituted for azathioprine in triple drug regimens. In a pooled efficacy analysis of three large, randomised, double blind, clinical trials of renal transplantation, the mycophenolate groups showed better survival of grafts and fewer rejection episodes (19.8% and 16.5% for mycophenolate 2 and 3 g *v* 40.8% for azathioprine, $p < 0.0001$).[11] There was no difference in infection rates between patients in the azathioprine group and the mycophenolate group.[11]

Three lung transplant centres recently reported their initial experience of mycophenolate mofetil in lung transplantation.[10] None of the studies was properly controlled, and each contained relatively small numbers of patients. All the studies reported significantly fewer episodes of acute rejection, proved by biopsy, without a significant increase in infection. In one paper the authors detected a significantly smaller drop in forced expiratory volume in one second in the mycophenolate group.[10]

Sirolimus (US approved name for rapamycin—Rapimmune, Wyeth, and RAD rapamycin derivative, Novartis) is structurally similar to tacrolimus but has a different mode of action.[12] Recently published phase II trials in renal transplant patients suggest that the drug can decrease acute rejection rates from 40% to less than 10% among patients taking full dose cyclosporin.[13] This improvement is achieved with a small, non-significant increase in infectious complications. The authors suggest that the drug may mitigate the need for long term steroid treatment.

Randomised controlled trials comparing mycophenolate mofetil and rapamycin or rapamycin derivative with azathioprine are now in the planning stages. These new drugs will soon form the basis of new immunosuppressive regimens for use in lung transplantation that are expected to have an impact on long term survival.

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NB is supported in part by the Sandoz study grant of the European Society of Transplantation.

1 Hosenpud JD, Novick RJ, Bennett LE, Keck BM, Fiol B, Daily OP. The Registry of the International Society for Heart and Lung Transplantation: thirteenth official report—1996. *J Heart Lung Transplant* 1996;15:655-74.
2 Bando K, Paradis IL, Similo S, Konishi A, Komatsu K, Zullo TG, et al. Obliterative bronchiolitis after lung and heart-lung transplantation. An analysis of risk factors and management. *J Thorac Cardiovasc Surg* 1995;110:4-13, 13-4.
3 Iacono AT, Keenan RJ, Duncan SR, Smalldone GC, Dauber JH, Paradis IL, et al. Aerosolized cyclosporine in lung recipients with refractory chronic rejection. *Am J Respir Crit Care Med* 1996;153:1451-5.
4 The International Society for Heart and Lung Transplantation 16th annual meeting and scientific sessions. New York, New York, March 15-18, 1996. Abstracts. *J Heart Lung Transplant* 1996;15:S1-114.
5 Dusmet M, Maurer J, Winton T, Kesten S. Methotrexate can halt the progression of bronchiolitis obliterans syndrome in lung transplant recipients. *J Heart Lung Transplant* 1996;15:948-54.
6 Chaparro C, Maurer JR, Chamberlain D, De Hoyos A, Winton T, Westney G, et al. Causes of death in lung transplant recipients. *J Heart Lung Transplant* 1994;13:758-66.
7 Mikhail G, Eadon H, Leaver N, Rogers P, Stephens D, Banner N, et al. An investigation of the pharmacokinetics, toxicity, and clinical efficacy of neoral cyclosporin in cystic fibrosis patients. *Transplant Proc* 1997;29:599-601.
8 Gjertson DW, Cecka JM, Terasaki PI. The relative effects of FK506 and cyclosporine on short- and long-term kidney graft survival. *Transplantation* 1995;60:1384-8.
9 Keenan RJ, Konishi H, Kawai A, Pradis I, Nunley DR, Iacono AT, et al. Clinical trial of tacrolimus versus cyclosporine in lung transplantation. *Ann Thorac Surg* 1995;60:580-4, 584-5.
10 The International Society for Heart and Lung Transplantation 17th annual meeting and scientific sessions. London, England, April 2-5, 1997. Abstracts. *J Heart Lung Transplant* 1997;16:41-142.
11 Halloran P, Mathew T, Tomlanovich S, Groth C, Hooftman L, Barker C. Mycophenolate mofetil in renal allograft recipients: a pooled efficacy analysis of three randomised, double-blind, clinical studies in prevention of rejection. The International Mycophenolate Mofetil Renal Transplant Study Groups. *Transplantation* 1997;63:39-47.
12 Brazelton TR, Morris RE. Molecular mechanisms of action of new xenobiotic immunosuppressive drugs: tacrolimus (FK506), sirolimus (rapamycin), mycophenolate mofetil, and leflunomide. *Curr Opin Immunol* 1996;8:710-20.
13 Kahan B. Sirolimus: a new agent for clinical renal transplantation. *Transplant Proc* 1997;29:48-50.

Continuing medical education: where next?

Doctors must manage their own education

The recent *BMJ* series on continuing medical education highlights the need for more efficient, up to date, and accountable programmes. Over the past three to four years the royal medical colleges in Britain have implemented their own schemes of formal continuing education. Adequate educational opportunities now exist for most British clinicians,[1] though much of the education offered is a diet of lectures, symposiums, and specialist society meetings. Given that lectures are not the ideal vehicle for adult learning, what other initiatives are available for practising doctors and what can we learn from new developments in Britain and world wide?

There are two ground rules. Firstly, every doctor has a personal responsibility to keep up to date and, secondly, trained professionals must be responsible for directing their own lifelong learning.[2 3] Accordingly, to help clinicians cope with the prodigious growth of information and to focus their effort, colleges and specialist societies have introduced, or are introducing, journal articles specifically designed for continuing medical education: many include an element of interaction between the reader and the topic which helps validate the learning. For example, the Royal College of Obstetricians and Gynaecologists has two paper based distance learning resources, PACE (personal assessment in continuing education) and LOGIC (learning in obstetrics and gynaecology for in-service clinicians), which provide up to date reviews written by experts and self assessment tests (PJD Milton, personal communication). It is now introducing a multimedia approach to distance learning.[4] The Royal College of Pathologists offers similar exercises and allows participants to compare their performance (anonymously) with that of their peers in the same specialty group.[5]

The profession is now well placed to reap the benefits of the electronic revolution. The medical knowledge self assessment programme of the American College of Physicians is now available on CD ROM, and interactive case based CD ROMs are also being distributed. Computer conferencing is increasingly being used, and educational programmes, such as that run by EuroTransmed, are delivered by satellite and on the internet. In Canada the innovative maintenance of competence programme (MOCOMP) of the Royal College of Physicians and Surgeons[6] encourages clinicians to manage their own continuing medical education using the philosophy that we should focus on what can be learnt from everyday practice. PCDiary software is used by participants to define their learning needs and to keep a portfolio of learning experiences.

We disregard many of the commendable, but underused, educational resources readily available within the NHS. Learning visits to experts or centres of excellence, not commonly regarded as formal education, can be of great practical help. If necessary these learning visits could be extended to longer secondments, particularly if consultants need to take new skills back to their own hospital. This type of challenge is being met by the Raven department of education at the Royal College of Surgeons of England, which teaches specialist skills to postgraduates and established consultants.

Peer review visits, pioneered and implemented by the Royal Australasian College of Physicians,[7] and now being pursued by several British specialist societies,[8] are manifestly of value to both the reviewed and the reviewers. Initial fears that they might prove hostile or intrusive have largely been dispelled, but the expense of site visits in America has been prohibitive.[9]

Continuing medical education doesn't just mean keeping up to date with one's own speciality interests. It has to be extended into the wider aspects of continuing professional development, including computer literacy, ethics, appraisal, management, and evidence based medicine. It also means facing the challenge of interprofessional collaboration and making teamwork a reality.[10] Striking the correct balance for each individual is not without difficulty.

The royal medical colleges have never regarded continuing medical education as a tool to deal with poor performance. With a fair system in place to help doctors who do not perform well,[11] continuing medical education should no longer be seen as a measure to identify bad doctors. It should be seen as prevention. The colleges' attention will remain focused on standards of medical care in a changing health service.

Questions remain whether continuing medical education should be mandatory. In Britain the colleges have agreed that formal schemes are necessary if they are to retain their self regulatory privileges. Self reporting systems are developing and compliance is high, but many doctors, while enjoying their education, find its documentation a chore. Few realistic and practical alternatives to formal college administered credit systems have, however, emerged. Fulfilment of educational requirements is no guarantee of clinical effectiveness or performance, but employers, insurers, and medicolegal agencies need to know that a doctor's continuing medical education is of good standing. If doctors are to be encouraged to "keep up to date" it is essential that time and reasonable funding are made available, particularly for those in the neglected non-consultant career grades.[12] Continuing medical education now needs to move on. Those who smugly reassure themselves by saying, "There's no need to change, we do it all anyway," will find themselves left behind.

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1 Crossley C, Toghill PJ. The provision of CME meetings for physicians. *J Roy Coll Physicians Lond* 1997;31:652-6.
2 Holm HA. Quality issues in continuing medical education. *BMJ* 1998;316:621-4.
3 Fox RD, Bennett NL. Learning and change: implications for continuing medical education. *BMJ* 1998;316:466-8.
4 Panikkar J. DIALOG. A new multimedia approach to distance learning in obstetrics and gynaecology. In: Learning Technology in Medical Education conference proceedings. *CTI Medicine* 1997:147-51.

BMJ 1998;316:721–2

5 Flynn FV. Development of distance learning for the college's CME scheme. *Bull Roy Coll Pathol* 1996;140:2-6.
6 Bashook PG, Parboosingh J. Recertification and the maintenance of competence. *BMJ* 1998;316:545-8.
7 Royal Australasian College of Physicians. Practice quality review. *Fellowship Affairs* 1996; Jul:17.
8 Page RL, Harrison BDW. Setting up interdepartmental peer review. *J Roy Coll Physicians Lond* 1995;29:319-24.
9 Richards T. Continuing medical education. *BMJ* 1998;316:246.
10 Headrick LA, Wilcock PH, Batalden PB. Interprofessional working and continued medical education. *BMJ* 1998;316:771-4.
11 Southgate L, Dauphinée D. Maintaining standards in British and Canadian medicine. The developing role of the regulatory body. *BMJ* 1998;316:697-700.
12 Macdonald R, Khan MA, Singleton C. Continuing medical education for associate specialists: results of a survey in Yorkshire. *BMJ* 1996;313:918.

Poverty in rural areas

Is more hidden but no less real than in urban areas

Rural societies are diverse, with a greater proportion of both people in higher socioeconomic groups and those with low pay than in urban populations.[1 2] Scattered among the relatively wealthy landowners, commuters, and professionals are rural dwellers living on very low incomes.[3 4] A recent *BMJ* editorial exhorted doctors to "combat the damage" of poverty.[5] In doing so, doctors should look beyond the rural idyll and recognise that, as elsewhere in the world, poverty in Britain is not confined to cities.

Carr-Hill et al emphasised the importance of looking at very small units—individuals and their families—when considering health needs.[6] This is particularly important in rural areas. In cities generalised observations about a street or electoral ward may be reasonably accurate, but in the country an affluent landowner and his socially isolated and underprivileged neighbour may be the only people for miles around.

Twenty per cent of the rural population of England and 25% of rural households live in "absolute poverty" (on an income of less than 140% of supplementary benefit entitlement).[2 7] In rural Scotland in 1994, 49% of heads of households had annual incomes below £7800 (half the median Scottish wage). In remote areas such as the Outer Hebrides the situation was worse, with almost the whole population on "poverty" incomes.[3] Elderly people are worst affected: 35% of poor rural households are elderly people living alone.

Employment trends help to explain such low incomes. The number of people employed in agriculture is decreasing. The trend is towards insecure, low paid, often part time work with limited potential for progression—for example, in tourism.[8] Only 38% of women in rural development areas have paid employment, compared with a British average of 45.5%.[1] Rural dwellers are less likely to register as unemployed and more likely to migrate in search of work.[2]

Contrary to popular belief, rural homelessness is a substantial problem. In England alone, over 46 000 people, 11.6% of the country's homeless, are in rural areas.[9] The popularity of second homes and retirement homes has led to inflated property prices, unattainable by young people. Rented accommodation may be available only during winter, out of the tourist season. The sale of council houses has reduced the availability of low cost housing for rent.[4]

Townsend describes poverty as "financial inability to participate in the everyday styles of living of the majority."[10] The more recent, broader concept of "social exclusion," developed within the European Union, may be more helpful. It shifts the focus from income and expenditure to multidimensional disadvantage, relating the individual to the society in which he or she lives.[11] Despite an increase in the size of many villages, services such as shops, schools, banks, police stations, and pubs have diminished.[12] People without their own transport and those with mobility problems have increasing difficulty in gaining access to services and are forced to use those local services that remain. They spend more per item at village stores than those who can drive to supermarkets. The rural rich can economise in ways that their poorer neighbours cannot. Similarly, independent transport is an expensive necessity in remote areas (77% of rural households have a car compared with an English average of 68%[1]) and compounds the poverty of families on low incomes. The popular image of poor rural dwellers being uncomplaining seems to be true. Many compare their situation with the harsher conditions of the past rather than with the current lifestyles of the majority.[3] Our knowledge of rural health need is limited,[13] but it is both logical and justifiable to assume that poverty and poor health are associated in rural areas,[14] just as they are in our towns and cities. We should not be blinded by the fact that rural poverty is hidden.

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1 Shucksmith M, Roberts D, Scott D, Chapman P, Conway E. *Disadvantage in rural areas*. Salisbury: Rural Development Commission, 1996.
2 Cloke P, Milbourne P, Thomas C. *Lifestyles in rural England*. Salisbury: Rural Development Commission, 1994.
3 Joseph Rowntree Foundation. *Disadvantage in rural Scotland*. York: Joseph Rowntree Foundation, 1994. (Social Policy Research 62.)
4 Skerratt S, Chapman P, Shucksmith M. *Disadvantage in rural and urban Allerdale*. Aberdeen: Arkleton Centre for Rural Development Research, 1996.
5 Haines A, Smith R. Working together to reduce poverty damage. *BMJ* 1997;314:529-30.
6 Carr-Hill RA, Rice N, Roland M. Socio-economic determinants of rates of consultation in general practice based on fourth national morbidity survey of general practices. *BMJ* 1996;312:1008-12.
7 Bradley A. Poverty and dependency in village England. In: Lowe, Bradley, Wright, eds. Disadvantage and welfare in rural areas. Norwich: Geo Books, 1987.
8 Townsend A. New forms of employment in rural areas: a national perspective. In: Champion and Watkins, eds. *People in the countryside*. London: Paul Chapman Publishing, 1991.
9 Rural Development Commission. *Homelessness in rural England: update to 1992/93*. London: Rural Development Commission, 1994.
10 Townsend P. *Poverty in the United Kingdom*. Harmondsworth: Penguin, 1979.
11 Room G. *Beyond the threshold: the measurement and analysis of social exclusion*. Bristol: Policy Press, 1995.
12 Rural Development Commission. *Survey of rural services*. London: Rural Development Commission, 1994.
13 Cox J. Rural general practice. *Br J Gen Prac* 1994; 44:388.
14 Phillimore P, Reading R. A rural advantage? Urban/rural health differences in northern England. *J Publ Health Med* 1992;14: 290-9.

BMJ 1998;316:722