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Brain damage in divers

Diving itself may cause brain damage—but we need more evidence

See p 701

Diving involves risk of neurological injuries. These may arise from decompression illness (a label which recognises the difficulty in distinguishing clinically decompression sickness due to gas nucleation from gas invasion caused by pulmonary barotrauma), anoxia (caused by near drowning), and the toxic effects of high partial pressures of breathing gases. The possibility that divers and others working in hyperbaric conditions may acquire neuropsychological damage without a clear history of a precipitating event is worrying. Since 1978 five international meetings have discussed this possibility, but no consensus exists whether diving per se causes brain damage.

Much of the evidence of functional abnormalities in divers with no history of decompression illness is anecdotal. Many reports describe findings in mixed groups of divers, some with and some without prior decompression illness.[1 2] The most quoted study involved a snapshot assessment of intellectual function in Australian abalone divers,[3] with no assessment of change over time and no controls. The psychological assessment probably failed to reflect the characteristics of these particular individuals, and their dive practices.

Nevertheless, degeneration and vasculopathy are seen after death in the brains and spinal cords of unaffected divers which resemble the abnormalities found after decompression illness.[4 5] Retinal fluorescein angiography in divers with no history of decompression illness has demonstrated vasculopathy, which may be a marker for neurovascular injury.[6] Concern is heightened by evidence of long term injuries to other organs, such as crippling dysbaric osteonecrosis in divers and caisson workers years after hyperbaric exposure.

When neurological damage occurs in divers the prime suspects are gas bubbles. Gas nucleation is generally accepted to be the initiating event in most of the syndromes collectively known as decompression sickness. However, free gas does not invariably lead to decompression sickness. Doppler ultrasound can detect "silent" bubbles in the venous blood of many asymptomatic divers. Most bubbles are filtered out by the pulmonary capillaries. It was once believed that a critical amount of gas nucleation was required before decompression sickness occurred. We now know that this may be true for extreme decompressions in individuals without intracardiac or pulmonary right to left shunts, but in those with a shunt a relatively small bubble load can result in paradoxical gas embolism.[7 8]

Decompression sickness can affect many systems, but the serious effects are neurological. There is usually abrupt or rapid evolution of a focal central neurological deficit (or deficits). The injury may be mild or severely disabling; it may be permanent or resolve spontaneously or with treatment with oxygen and recompression; episodes may recur. Clinically the spectrum of neurological decompression sickness resembles that of thromboembolic cerebrovascular disease, with one exception: decompression sickness commonly affects the spinal cord. This difference may be explained by the considerable gas load in the cord at the end of many dives compared with the gas content of an equivalent weight of brain tissue. The greater blood flow to the brain means that more gas bubbles embolise the brain, but more dissolved gas is available to amplify embolic bubbles in the cord. Conceivably recurrent subclinical decompression sickness may result in a condition analogous to multi-infarct dementia with gas embolism rather than thromboembolism as the initiator.

There are other neurological insults. During many normal dives neurological effects occur from variations in gas partial pressures. Every depth change of 7 m produces change in ambient pressure equivalent to a trip between sea level and the top of Mount Everest. The narcotic effects of nitrogen at depths of 30 m or less are well described. Narcosis is reversed by ascent but can repeated exposure cause target organ damage like repeated alcohol intoxication? Other breathing gases are also not inert at high partial pressures. Oxygen is neurotoxic. Very deep dives, during which mixtures containing helium are breathed, can result in the high pressure neurological syndrome, which causes excitatory effects including tremor, myoclonus, and convulsions. Repeated insults might produce permanent harm.

Until recently investigational techniques were too insensitive to detect neurological abnormalities in "normal" divers or even in those with clinical effects from decompression illness[9]. Magnetic resonance imaging seems to offer greatest promise. Reul and colleagues found more hyperintense subcortical white matter lesions in the brains of sport divers than in non-diving controls.[10] The difference was due to a subgroup of divers who had multiple brain lesions. In this issue Knauth and colleagues report that multiple brain lesions on magnetic resonance scans in sport divers occur exclusively in those with large right to left shunts (presumed to be patent foramen ovale, though some

may be small atrial septal defects or pulmonary arteriovenous shunts) (p 701).[11]

These observations are consistent with the well documented role of shunts in the pathogenesis of overt decompression illness by means of paradoxical gas embolism but extend this role to subclinical injury. This is plausible. Decompression illness is a spectrum. It may be so mild that divers do not seek treatment.[8] Divers who have had decompression illness and in whom we find a large shunt often recollect mild neurological symptoms after earlier dives which they did not consider important at the time. The fact that the illness can be mild adds plausibility to studies showing an increased prevalence of subclinical lesions in divers with a large shunt but also cautions against accepting data uncritically from studies in which subjects were self selected.[10 11]

The results of magnetic resonance scans in others exposed to hyperbaric conditions have not been entirely consistent. Caisson workers also have an increased prevalence of brain lesions.[12] Professional divers do not,[13] even though necropsy evidence of pathological injury is commoner than in sport divers.[5] Magnetic resonance imaging does not always reveal abnormalities in cases of clear neurological decompression illness.[14] These apparent contradictions may be due to differences in imaging techniques, methods of subject recruitment, and confounding variables. Interestingly, magnetic resonance findings do not correlate with the results of psychometric tests or electroencephalograms.[12 13] Further investigation into the possibility that diving per se causes brain damage is required, but we must not forget that evidence of pathological change is not proof of functional deficit.

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1 Vaernes RJ, Eidsvik S. Central nervous dysfunctions after near miss accidents in diving. *Aviat Space Environ Med* 1982;53:803-7.
2 Todnem K, Nyland H, Skiedsvoll H, Svihus R, Rinck P, Kambestad BK, *et al.* Neurological long term consequences of deep diving. *Br J Indust Med* 1991;48:258-66.
3 Edmonds C, Boughton J. Intellectual deterioration with excessive diving (punch drunk divers). *Undersea Biomed Res* 1985;12:321-6.
4 Palmer AC, Calder IM, Hughes JT. Spinal cord degeneration in divers. *Lancet* 1987;ii:1365-6.
5 Palmer AC, Calder IM, Yates PO. Cerebral vasculopathy in divers. *Neuropathol Appl Neurobiol* 1992;18:113-24.
6 Polkinghorne PJ, Sehmi K, Cross MR, Minassian D, Bird AC. Ocular fundus lesions in divers. *Lancet* 1988;ii:1381-3.
7 Moon RE, Camporesi EM, Kisslo JA. Patent foramen ovale and decompression sickness in divers. *Lancet* 1989;i:513-4.
8 Wilmshurst PT, Byrne JC, Webb-Peploe MM. Relation between interatrial shunts and decompression sickness in divers. *Lancet* 1989;ii:1302-6.
9 Halsey MJ, Elliott DH, eds. *Diagnostic techniques in diving neurology.* London: Medical Research Council Decompression Sickness Panel, 1987.
10 Reul J, Weis J, Jung A, Willmes K, Thron A. Central nervous system lesions and cervical disc herniations in amateur divers. *Lancet* 1995;345:1403-5.
11 Knauth M, Ries S, Pohlmann S, Kerby T, Forsting M, Daffertshofer M, *et al.* Multiple brain lesions in sport divers: the role of a patent foramen ovale. *BMJ* 1997;314:701-5.
12 Fueredi GA, Czarnecky DJ, Kindwall EP. MR findings in the brains of compressed-air tunnel workers: relationship to psychometric results. *AJNR* 1991;12:67-70
13 Todem K, Skeidsvoll H, Svihus R, Rinck P, Riise T, Kambestad BK, *et al.* *Electroenceph Clin Neurophysiol* 1991;79:322-9.
14 Warren LP, Djang WT, Moon RE, Camporesi EM, Sallee DS, Anthony DC, *et al.* Neuroimaging of scuba diving injuries to the CNS. *AJR* 1988;151:1003-8.

Dopamine in oliguria

Should be used for specific conditions, not as prophylaxis

Renal failure often manifests as oliguria. Many therefore view oliguria as a sinister development that should be prevented or treated in the hope of avoiding renal failure. However, oliguria can be a normal physiological response and, in itself, is a poor predictor of acute renal failure.[1 2] Nevertheless, dopamine infusions have gained popularity over the past 20 years as a means to prevent or treat oliguria.

Dopamine is usually infused at low to intermediate rates of 2-5 μg/kg/min. The perceived beneficial effects include increased cardiac output, improved renal perfusion, reduced tubular metabolic activity, diuresis, and natriuresis. Thus, dopamine is used in a variety of clinical settings to prevent or ameliorate renal injury or hasten restoration of renal function.[3 4] Cardiac failure and fluid overload have also been considered as indications for dopamine, although tachyphylaxis may limit these potential benefits.[4]

Recently, there has been a greater focus on potential adverse effects.[5] Arrhythmias and myocardial, gut, and peripheral vascular ischaemia are well described. Other potential harmful effects include dopamine induced diuresis in the presence of volume depletion, pulmonary hypertension, impaired hypoxic ventilatory responses, decreased gastric motility, increased metabolic rate, and increased weight loss. Dopamine also causes endocrine and immune dysfunction, with reduced secretion of growth hormone, prolactin, and dehydroepiandosterone.[6]

Reduced secretion of growth hormone may promote catabolism and impair immune responses. Hypoprolactinaemia and low dehydroepiandosterone also impair cellular immune responses as a result of reduced T cell proliferation and effects on T helper cells.[6 7] Importantly, reduced cellular immune responses are strongly associated with sepsis related mortality in patients receiving intensive care after emergency surgery.[8] Thyroid function is also impaired.

Other hidden costs include central venous cannulation with its attendant risks,[9] the need for infusion and monitoring equipment, and increased nursing and medical supervision. The assumption that dopamine may be beneficial but will do no harm is questionable, and its use as prophylaxis means that many patients who are exposed will never benefit. Since it is impossible to balance benefits against risks from small explanatory trials, studies of clinical outcomes are vital to judge whether dopamine infusions confer net benefit as prophylaxis or as treatment for oliguric states.

Denton concluded that there was little good published evidence to support the use of low dose dopamine infusions to prevent acute renal failure in high risk patients or to ameliorate the clinical course of established acute renal failure.[4] However, these outcome studies are very small with little power even for the surrogate outcomes,[4] and potential benefits might be overlooked.[10] Many are too small to address clinically meaningful outcomes such as the long term renal function, the need for renal replacement therapy, and survival.

The present uncertainty regarding the benefits and risks of dopamine infusions is surely unacceptable. This uncertainty cannot be resolved by using surrogate markers because they often fail to predict the overall effect on clinical outcome.[11] Observational studies are weakened by bias and confounding factors and cannot be relied on to resolve clinical controversies.[12] The time has come for large scale, randomised controlled trials to be funded and conducted in the various settings in which dopamine is used so that doctors can confidently identify when dopamine has a real and rational role.

Given our existing knowledge, any recommendations on the indications for low dose dopamine[13] will inevitably be based more on opinion than evidence, but some guidance may be helpful. In our opinion, dopamine should not be used as a prophylactic agent except in specific situations in which there is some evidence of benefit.[10] It should be reserved for individual clinical situations where its diuretic and inotropic properties might be of use. If there are side effects, or no beneficial effects, the infusion should be stopped.[13] The need for a good evidence base to guide the rational use of dopamine is paramount.

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1 Sweny P. Is postoperative oliguria avoidable? *Br J Anaesth* 1991;67:137-45.
2 Kellen M, Aronson S, Roizen MF, Barnard J, Thisted RA. Predictive and diagnostic tests of renal failure: a review. *Anesth Analg* 1994;78:134-42.
3 Seri I. Cardiovascular, renal, and endocrine actions of dopamine in neonates and children. *J Pediatr* 1995;126:333-44.
4 Denton MD, Chertow GM, Brady HR. "Renal-dose" dopamine for the treatment of acute renal failure: scientific rationale, experimental studies and clinical trials. *Kidney Int* 1996;49:4-14.
5 Thompson BT, Cockrill BA. Renal-dose dopamine: a siren song. *Lancet* 1994;344:7-8.
6 Van den Berghe G, deZehger F. Anterior pituitary function during critical illness and dopamine treatment. *Crit Care Med* 1996;24:1580-90.
7 Devins SS, Miller A, Herndon BL, O'Toole L, Reisz G. Effects of dopamine on T-lymphocyte proliferative responses and serum prolactin concentrations in critically ill patients. *Crit Care Med* 1992;20:1644-9.
8 Christou NV, Meakins JL, Gordon J, Yee J, Hassan-Zahree M, Nohr CW, *et al.* The delayed hypersensitivity response in surgical patients. 20 years later. *Ann Surg* 1995;222:534-48.
9 Kaye CG, Smith DR. Complications of central venous cannulation. Trauma, infection, and thrombosis. *BMJ* 1988;297:572-3.
10 Memoli B, De Nicola L, Libetta C, Scialo A, Pacchiano G, Romano P, *et al.* Interleukin-2-induced renal dysfunction in cancer patients is reversed by low-dose dopamine infusion. *Am J Kidney Dis* 1995;26:27-33.
11 Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? *Ann Intern Med* 1996;125:605-13.
12 Tumar KJ, Roizen MF. Outcome assessment and pulmonary artery catheterization: why does the debate continue? *Anesth Analgesia* 1997;84:1-4.
13 Bonde J, Lauritsen LM, Kamp-Jensen M, Olsen NV. Low dose dopamine in surgical and intensive care patients. *Acta Anaesthesiol Scand* 1996;40:326-30.

Compliance becomes concordance

Making a change in terminology produce a change in behaviour

See p 747

At long last the "compliance problem" may be getting a new name and, with it, a new view of the patient's role in the doctor-patient relationship. A report published this week by the Royal Pharmaceutical Society of Great Britain's working party on medicine taking recommends that "concordance" should replace the term "compliance."[1] Although substitute terms have been suggested and used previously without much impact, this eloquent analysis of the importance of a new concept by a highly visible and distinguished panel may hold the promise of change. Moreover, the panel recommends a £1.8m ($2.7m) research budget to support analysis of the problem and training of health professionals.

Compliance has long been criticised as denoting obedience—"following doctors' orders." Although many researchers and practitioners have carefully avoided the term,[2] the common alternatives—"adherence" or "cooperation"—do not take the user very far from compliance. One member of the working party, David Sackett, in his 1976 landmark publication, *Compliance with Therapeutic Regimens,* had already anticipated the approach advocated by the Pharmaceutical Society's report.[3] Included in the book were sensible ideas such as the "tailored consensual regimen," the need for a no fault approach to behaviour relating to following a regimen,[4] and consideration of the effect of frequency of administration, side effects, delivery system, and the like—all aspects of the medication that affect compliance.[5] A subsequent publication raised the idea of a clinically relevant definition of adherence, based on the properties of a particular drug and not solely on the doctor's instructions.[6] Thus if seven days are sufficient to achieve the therapeutic effect of a drug then patients who stop the medication after "only" seven, eight, or nine days should not be deemed to be non-compliant even if it was prescribed for 10 days.

Despite the predominance of the term compliance, interventions have not all been aimed at the patient. Manufacturers, for example, have responded with less complex delivery mechanisms such as patches, more convenient doses such as sustained release drugs, incentives for patients to fill their first prescription and to get refills, advertising to increase the perceived value of the drug, and direct patient education. In part these developments indicate that the manufacturers understand clearly the effects of non-compliance on drug

sales. But they also suggest that clinicians value drugs with features that enhance compliance.

Changes in drug trials reflect recognition of the effect of compliance on statistical power and interpretation of results.[7,8] After initial resistance to including compliance experts, some investigators began to include them when planning the trial rather than attempting to fix problems later.[9] Another approach has been pre-randomisation screening of potential participants, usually with a placebo. This approach assumes that non-compliance is a general characteristic of the person: thus a pretrial test of drug taking can reveal non-compliers.

The change in terminology will have an impact only if the culture change that the working group is advocating succeeds and clinicians take a more egalitarian view "of the relationship between prescribing and medicine-taking, between patient and prescriber."[10] It is possible to envisage doctors and patients engaging in more productive discussion of medication regimens, but the barriers are substantial. A prescription is a traditional means of ending a consultation, after most of the time has been spent on diagnosis. Perfunctory questioning about the drug at the next visit may lead patients to assume that the doctor does not place high priority on drug taking. Clinicians may simply assume the patient's compliance and see any continuing symptoms as indicating the need for more or a different medication.

More time spent should be spent assessing not only the best medication for a particular condition but also the best for a particular individual with a certain lifestyle and preferences. The concept of concordance suggests frank exchange of information, negotiation, and a spirit of cooperation. Compared with the US, conditions in Britain favour this approach. Patients and practitioners are more likely to have known one another for longer, dispensing is less impersonal, and ancillary personnel are available for follow up.

Moreover, evidence of effectiveness is available from rigorous trials, and no single method of improving compliance appears to be inherently superior.[11] With coaching and a non-judgmental attitude from the prescriber, patients are more likely to describe drug taking truthfully. Patients can be informed about dosing options and asked what would work best for them. Initial prescriptions can be regarded as a trial, not only of the drug's effect but also of the feasibility of taking it. Treating the patient as a decision maker is a fundamental step away from the compliance model.

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1 Royal Pharmaceutical Society of Great Britain. *From compliance to concordance: towards shared goals in medicine taking*. London: RPS, 1997.
2 Shumaker SA, Schron EB, Ockene JK. *The handbook of health behavior change*. New York: Springer, 1990.
3 Sackett DL. Introduction. In: Sackett DL, Haynes RB, eds. *Compliance with therapeutic regimens*. Baltimore: Johns Hopkins University Press, 1976.
4 Fink DL. Tailoring the consensual regimen. In: Sackett DL, Haynes RB, eds. *Compliance with therapeutic regimens*. Baltimore: Johns Hopkins University Press, 1976.
5 Fitzgerald JD. The influence of the medication on compliance with therapeutic regimens. In: Sackett DL, Haynes RB, eds: *Compliance with therapeutic regimens*. Baltimore: Johns Hopkins University Press, 1976.
6 Haynes RB, Taylor DW, Sackett DL. *Compliance in health care*. Baltimore: Johns Hopkins University Press, 1979.
7 Rudd P, Ahmed S, Zachary V, Barton C, Bonduelle D. Antihypertensive drug trials: Contributions from medication monitors. In: Cramer JA, Spilker B, eds. *Patient compliance in medical practice and clinical trials*. New York: Raven Press, 1991.
8 Urquhart J. Patient compliance as an explanatory variables in four selected cardiovascular studies. In: Cramer JA, Spilker B, eds. *Patient compliance in medical practice and clinical trials*. New York: Raven Press, 1991.
9 Russell ML, Insull W, Jr. Evaluation and training of medication adherence counselors in a clinical trial: application of a skill inventory to video-recorded interviews. *Controlled Clinical Trials* 1981:2:133-48.
10 Marinker M. From compliance to concordance: achieving shared goals in medicine taking. *BMJ* 1997:314:747-8.
11 Mullen PD, Green LW, Persinger G. Clinical trials of patient education for chronic conditions: A comparative meta-analysis of intervention types. *Prev Med* 1985:14:753-81.

Training senior house officers

The lost tribes are still in the wilderness—and breeding

See pp 713, 719, 740

In the film *Annie Hall* Woody Allen tells an aphorism about two elderly ladies at a health farm. "The food here is really terrible," says one to her friend. "Yes, and such small portions," comes the reply. So it is with senior house officer training.

Two years ago the conference "Senior house officers: the lost tribes" discussed the problems with training.[1] The Calman report[2] and a report due from the General Medical Council[3] address the concerns relating to the training of higher specialist trainees and preregistration house officers respectively. The Academy of Royal Colleges' recently published report on senior house officer training[4] has joined a long list of similar expressions of concern.[5-8] "Service based training" has been promoted as the answer to the tension between service and training requirements. This differs from the traditional random exposure to clinical work of variable relevance and ad hoc (or no) supervision in that it involves crucial components such as feedback, appraisal, and the setting of educational objectives.[8] Its introduction has been slow, although, as Paice *et al* report this week some progress has been made.[9]

No amount of educational enlightenment about "service based training" and appraisal, however welcome, will solve the problems of training senior house officers if posts continue to be created primarily for the purpose of delivering service. Senior house officers represent cheap labour to the NHS. They are particularly valuable for out of hours emergency care because their role as the resident "safety net," while partly designed to protect patients, also protects consultants, and in some cases higher trainees, from providing immediate out of hours service or directly supervising preregistration house officers.

Limits to the number of senior house officer posts were removed in 1994.[10] The number of posts

subsequently increased by 740 (5%) in 1995 and by 480 in 1996-7.[11] The number of "pseudo-senior house officer posts"—unapproved posts funded wholly by trusts to do service work—has also risen.

In 1994 regional task forces and deans were given the power to approve new posts in order to implement the new deal.[10] However, new senior house officer posts should have been a last resort, with priority given to funding new consultant posts to substitute for lost service due to restrictions on hours of work, to enhance training, and to encourage the development of a consultant based service. Consultant expansion has been insufficient,[12] and the intended change in the role of the consultant has also been slow to evolve. The growth in approved and unapproved senior house officer posts has outstripped the supply of doctors to fill them. Vacancies result in incomplete rotas which breach the hours limits or require the use of expensive locums.

Extra posts have also been requested by trusts, sometimes at the suggestion of the royal colleges, with the stated aim of improving training. When exposure to supervised training is poor the remedy is rarely more posts, particularly in the surgical specialties, where senior house officers are already competing for operative experience and supervision. A better solution is to redistribute posts to sites where there are more cases and fewer higher trainees (such as district general hospitals), to provide more consultants to enhance supervision, or to appoint service grades (including nurse practitioners) to reduce excessive workloads.

Expansion of the senior house officer grade worsens the bottlenecks at entry to higher specialist training. Again, the numbers of specialist registrars should be increased using funds currently being spent on new senior house officer posts. Indeed, the conversion of "excess" senior house officer posts to specialist registrar posts would help achieve this aim, and in so doing fuel the much needed expansion in consultant numbers.

Removing senior house officer posts may be felt to threaten the reductions achieved in junior doctors' hours, but existing rotas would be preserved by allowing specialist registrars to share out of hours rotas with the remaining senior house officers. This would also allow the higher trainees—consultants of the future—to retain those "hands on" emergency skills which their predecessors may have lost.

Recently the NHS Executive has issued a directive to postgraduate deans not to fund new senior house officer posts and not to approve any fully funded by a trust.[11] Because of the value for money that these doctors provide for trusts, however, the withdrawal of the deans' 50% contribution to salaries is unlikely to deter the establishment of unapproved posts.

It is also essential to increase the deans' contributions to 100% of basic salary and to ensure that trusts do not continue to create unapproved posts. In return for this increased power to control numbers, deans would have to be more accountable for the quality of the posts they fund. They would have to make annual inspections and be prepared to withdraw approval from departments with unapproved posts and from posts that did not meet adequate standards on hours, accommodation, or training.

The efforts invested in improving the preregistration year and higher specialist training will be wasted if the potential of the intervening grade—containing the largest number of doctors—is not fully realised.

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1 Dillner L. Senior house officers: the lost tribes. *BMJ* 1993;307:1549-51.
2 Working Group on Specialist Medical Training. *Hospital doctors: training for the future*. London: Department of Health, 1993.
3 General Medical Council, Education Subcommittee. *The new doctor*. London: GMC (in press).
4 Academy of Royal Colleges. *Recommendations for training for senior house officers*. London: Academy of Royal Colleges (in press).
5 Standing Committee on Post-graduate Medical Education. *Improving the experience: good practice in SHO training*. London: SCOPME, 1991.
6 M Baker. Enhancing the educational content of SHO posts. *BMJ* 1993;306:808-9.
7 *Training in medicine for the SHO. 1994. A joint report by the Royal College of Physicians of Edinburgh, Royal College of Physicians and Surgeons of Glasgow, Royal College of General Practitioners*. London: RCP, 1994.
8 COPMED, UK Conference of Deans. *SHO training: tackling the issues, raising the standards*. London: COPMED, 1995.
9 Paice E, West G, Cooper R, Orton V, Scotland A. Senior house officer training: is it getting better? *BMJ* 1997;314:719-20.
10 NHS Executive. *Implementing the new deal*. London: Department of Health, 1994 (Executive letter (94) 17).
11 NHS Executive. *Funding postgraduate medical and dental education in 1997/98*. London: Department of Health, 1997 (Executive letter (97) 10).
12 Brearley S. The failure of consultant expansion. *BMJ* 1994;309:1245-6.

Drug treatments for Alzheimer's disease

Raise clinical and ethical problems

Since early January a new treatment for Alzheimer's disease—the acetylcholinesterase inhibitor donepezil—has been available in the United States[1] and last week was licensed in the UK. This and possibly other similar compounds will be introduced in the UK and other European countries shortly. Donepezil is the first drug to be licensed in the UK for Alzheimer's disease, and, while its benefits still appear modest, it is easily administered and its side effect profile appears favourable.[2] The availability of such drugs does, however, raise clinical and ethical issues.

In 30 week clinical trials a range of cholinesterase inhibitors have been shown to have broadly similar efficacy.[2-3] These trials, designed to evaluate symptomatic treatment for Alzheimer's disease, have used two outcome measures: a sensitive measure of cognitive

function (ADAS-Cog[5]) and a global measure of change rated by a clinician independent of the study and blind to all other measures (CIBIC[6]). Results, on average, have been a 4-6 point difference on the ADAS-Cog scale between treatment and control groups, equivalent to about six months' delay in the course of the disease. Similarly, the independent clinical impression, after six months' treatment, was that significantly more of those treated with the drug showed either no deterioration or an improvement.

Patients included in the clinical trials had to have uncomplicated mild to moderate Alzheimer's disease. Therefore interpreting and applying these findings to the clinical setting is problematic. Only clinical experience with these compounds will indicate their true usefulness. For people with Alzheimer's disease and their carers the benefits of these drugs will be determined by their ability to improve everyday functioning and quality of life.

Cholinesterase inhibitors are a specific treatment for Alzheimer's disease, rather than dementia in general. In recent years the diagnostic challenges have increased with the recognition of dementia of the Lewy body type[7] and frontal lobe dementia.[8] Definitive diagnosis requires specialised skills, knowledge,[9] and investigations such as neuroimaging. A survey of carers of people with dementia showed that the diagnosis of Alzheimer's disease is haphazard and may be made by the patient's general practitioner, a specialist (neurologist, geriatrician, or psychogeriatrician), or not at all.[10] The availability of drugs will increase the likelihood of patients coming forward, and trial data suggest that these drugs are most likely to benefit patients early in the disease. Primary care practitioners will have to respond to these patients in new ways.

Treatment protocols will be necessary to ensure an equitable distribution of resources. Currently none exist. Those who develop protocols should ensure wide consultation, particularly with patients and carers. Without coordinated discussion, regional variations in prescribing are likely to develop.

No scientific data exist on the effects of stopping treatment with a cholinesterase inhibitor. Patients who took part in the clinical trials continued to take the active drugs with no defined end point. Without controlled data on long term treatment and treatment discontinuation, the decision to stop the drug may be clinically and ethically difficult to make.

The best available estimate of the costs of providing health and social services to people with Alzheimer's disease in England was £1.1 bn ($1.8 bn).[11] Not surprisingly drug expenditure on patients with dementia is low,[12] comprising mainly antidepressants, neuroleptics, and hypnotics. The introduction of specific drugs for Alzheimer's disease will increase demand on the drugs budget and shift the burden towards primary health care.

It has been argued that drug treatment for Alzheimer's disease will reduce the need for community support and delay entry into institutional care. One measurable economic outcome examined in open studies of tacrine, an earlier cholinesterase inhibitor, is a delay in institutionalisation. Two American studies suggested that the drug delayed entry into institutional care by up to nine months with an overall saving of 17-30%.[13,14] However, delaying institutionalisation may simply shift the burden to the community and families. Moreover, if the drug prolongs the duration of illness then costs will be increased for both health and community services.

The advent of drug treatments for Alzheimer's disease has major implications for the NHS and social services departments as well as patients and their carers. Considerable thought needs to be given to early and accurate diagnosis, the selection of patients most likely to benefit, the impact on primary care, and the overall cost to health and community care budgets. Ethical issues will arise over any lack of equity caused by the use of different treatment protocols, the continuation and discontinuation of treatment, and the impact on the individual and family members of possibly increasing the duration of the illness. We need both more evidence from the use of these drugs in practice and an informed public debate on the issues.

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1 Eisai's Aricept launches in the US. *Scrip* 1997;2198:17.
2 Rogers SL, Friedhoff LT. The efficacy and safety of donepezil in patients with Alzheimer's disease. Results of a US multicentre, randomized, double-blind, placebo-controlled trial. *Dementia* 1996;7:293-303.
3 Knapp MJ, Knopman DS, Solomon PR, Pendlebury WW, Davis CS, Gracon SI. A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. The Tacrine Study Group. *JAMA* 1994;271:985-91.
4 Thal LJ, Schwartz G, Sano M, Weiner M, Knopman D, Harrell L, *et al.* A multicenter double-blind study of controlled-release physostigmine for the treatment of symptoms secondary to Alzheimer's disease. *Neurology* 1996;47:1389-95.
5 Rosen WG, Mohs RC, Davis K. A new rating scale for Alzheimer's disease. *Am J Psychiatry* 1984;141:1356-64.
6 Leber P. *Guidelines for the clinical evaluation of antidementia drugs.* Rockville MD: US Food and Drug Administration, 1990.
7 McKeith IG, Fairbairn AF, Perry RH, Thompson P. The clinical diagnosis and misdiagnosis of senile dementia of Lewy body type (SDLT). *Br J Psychiatry* 1994;165:324-32.
8 The Lund and Manchester Groups. Clinical and neuropathological criteria for frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 1994,57:416-8.
9 Kelly CA, Harvey RJ, Stevens SJ, Nicholl CG, Pitt BMN. Specialist memory clinics; the experience at the Hammersmith Hospital. *Facts and Research in Gerontology* 1995,1:21-30.
10 *Right from the start.* London: Alzheimer's Disease Society, 1995.
11 Gray A, Fenn P. Alzheimer's disease: the burden of the illness in England. *Health Trends* 1993;25:31-7.
12 NHS Executive. *Burdens of disease: a discussion document.* Leeds: Department of Health, 1996.
13 Knopman D, Schneider L, Davis K, Talwalker S, Smith F, Hoover T, *et al.* Long-term tacrine (Cognex) treatment: effects on nursing home placement and mortality, Tacrine Study Group. *Neurology* 1996,47:166-7.
14 Lubeck DP, Mazonson PD, Bowe T. Potential effects of Tacrine on expenditure for Alzheimer's disease. *Medical Interface* 1994;7:130-8.