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EDITORIALS

Renal complications of childhood type 1 diabetes

Are correlated with glycated haemoglobin, so tight control is needed from the start



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RESEARCH, p 697

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The primary goal of managing childhood type 1 diabetes is to prevent or delay retinal and renal microvascular complications. Because lesions are silent for a long time,¹ glycated haemoglobin (HbA_{1c}) concentrations are used as a surrogate measure of the adequacy of treatment to avoid diabetic complications. Most of our knowledge of the relation between control of diabetes and the risk of renal complications of diabetes comes from data in adults and adolescents, so it is important to have a precise evaluation of the risk in children.

In the accompanying paper, Amin and colleagues report on the risk of diabetic renal disease in the Oxford regional prospective study, a population based cohort study of children with type 1 diabetes.² The prevalence of microalbuminuria was about 25% and 50% after 10 and 20 years of diabetes, respectively. The natural course of microalbuminuria was such that about half of patients reverted at least transiently to normoalbuminuria and 13% progressed to macroalbuminuria. The study answers important questions for those who care for children with diabetes.

The main result of the study is that mean HbA_{1c} is a strong predictor—and the only modifiable one identified—of microalbuminuria, with a hazard ratio of 1.39 (95% confidence interval 1.27 to 1.52), for each 1% increase of HbA_{1c}. The study did not directly assess whether an HbA_{1c} threshold existed, below which the risk of microalbuminuria is null or minimal. However, the group with a mean HbA_{1c} lower than 8.5%, the best controlled group of patients in the study, was not protected—these patients had around a 15% risk of microalbuminuria at the age of 20 years.

The role of the control of diabetes during childhood—as opposed to later in life—in determining the risk of complications is important because the complications of diabetes are first identified after the onset of puberty, even in patients with early onset of disease. In Amin and colleagues' study,² the prevalence of microalbuminuria was not influenced by the age of onset of diabetes after 15 years of disease, indicating that the deleterious effect of hyperglycaemia is similar in childhood and later in life. In apparent contradiction, a Finnish study found a lower risk of end stage renal disease after 30 years of diabetes in patients who were diagnosed before the age of 5 years.³ Further studies are needed to evaluate whether the rate of progression from microalbuminuria

to macroalbuminuria and renal insufficiency is influenced by the age at onset of diabetes.⁴

Are these results representative of the health of children with diabetes elsewhere? The mean HbA_{1c} of the cohort (9.8%) is higher than was seen in two large paediatric collaborative studies, which found a mean HbA_{1c} of 8.6-9%.^{5 6} However, neither of these studies was population based, so Amin and colleagues' results are probably an unbiased representation of care for childhood diabetes in Europe. They remind us that, in practice, we are far from the HbA_{1c} threshold of less than 7.5% in teenagers, 8% in children, and 8.5% in toddlers recommended by the American Diabetes Association—in their study, even the best controlled group of patients did not reach these thresholds.⁷

Other important predictors of diabetic kidney disease need to be considered.² Higher glucose variability for a given HbA_{1c} value has been proposed as an independent predictor of complications.⁸ Although the influence of glucose variability is controversial, it would be worthwhile examining this measure in Amin and colleagues' study. Individual factors—whether genetic or epigenetic—have an important role in modulating the risk of diabetic complications, and it will be essential to identify them as covariates to HbA_{1c}.^{9 10}

A small proportion of patients with microalbuminuria in the study were treated with antihypertensive drugs with rather unsatisfactory results. This finding should be interpreted with caution, however, because indications for use of antihypertensive drugs were not controlled, and compliance is often poor in adolescents and young adults with a long history of chronic disease. As discussed by the authors, no data are available on the use of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists in adolescents with diabetic nephropathy, and intervention trials are needed to evaluate whether treatments recommended for adults with microalbuminuria are similarly renoprotective in adolescents.¹¹

In summary, Amin and colleagues' study unequivocally shows that both recent and more remote concentrations of glycated haemoglobin are associated with the risk for microalbuminuria and progression from microalbuminuria to macroalbuminuria. They remind us that the future is dim for children with diabetes unless their disease is rigorously controlled

throughout childhood and adolescence by diet, education, adequate delivery of insulin, and control of blood glucose, while avoiding hypoglycaemia. Paediatricians are often torn between the inclination to reduce the pressure on patients and families and the need to use sophisticated but demanding treatments, such as multiple injections, pumps, and—more recently—continuous glucose monitoring.¹² These new data will certainly help doctors counsel their patients and families on treatment options that should more than ever focus on tight diabetes control with targets such as those recommended by the American Diabetes Association.

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Treatment of brucellosis

Regimens containing aminoglycosides are most effective but difficult to implement in practice

RESEARCH, p 701

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Although human brucellosis has been recognised for 121 years it remains difficult to treat.¹ It is transmitted mainly from domestic animals to humans through direct contact, contaminated animal products (particularly dairy products), and by inhalation of infectious particles. *Brucella* has developed many ways to evade the human immune system, and it induces a disease that is often relapsing or chronic. The geographical distribution of the disease is constantly changing, with new foci emerging,² and *Brucella* also has the potential to be used in biowarfare as it is easily produced in a steady aerosolised form.³ *Brucella's* unique interaction with the human immune system means that a protracted therapeutic regimen with a combination of antibiotics is needed to avoid treatment failure and relapses, serious complications, or residual damage from focal disease.^{4, 5} The optimal treatment regimen is debatable.

In the accompanying paper, Skalsky and colleagues report a systematic review of randomised controlled trials of different antibiotic regimens used for human brucellosis.⁶ Conducting such a review is no easy task because the trials assessed many combinations of antibiotics, which were given under different clinical conditions, for different periods, and for infections induced by strains with undefined and potentially different virulence.

Many of the trials recruited small numbers of patients, compared suboptimal regimens, used dubious diagnostic criteria, and inadequately evaluated

side effects (for example the nephrotoxicity and ototoxicity of aminoglycosides). Moreover, trials of brucellosis treatment have inherent pitfalls related to how therapeutic success is defined and the need for a long follow-up.⁷ Skalsky and colleagues have done an excellent job of tackling these shortcomings.

The authors conclude that a triple regimen of doxycycline, aminoglycoside, and rifampicin is the optimal combination (relative risk of failure compared with doxycycline-aminoglycoside 0.40, 95% confidence interval 0.20 to 0.79). This conclusion is based on just two randomised controlled trials, the first of which was undertaken in patients with spondylitis—a complication of brucellosis that is notoriously difficult to treat.⁵ Most specialists agree that brucellar spondylitis has to be targeted aggressively and early to minimise harm, although this does not apply to the treatment of brucellosis in general. The second trial, in contrast, found no significant difference between double and triple regimens.

So how should we interpret these results? Eventually it goes back to the long standing dilemma about treating brucellosis—whether to combine doxycycline with a parenteral aminoglycoside or with rifampicin. Skalsky and colleagues' conclusions emphasise previous observations that it is best to include an aminoglycoside in the therapeutic regimen (either streptomycin or gentamicin, although for gentamicin the duration of administration is still vaguely defined).

Despite the thorough analysis it is unclear how the

results of the review translate into everyday clinical practice. A study of patients with brucellosis showed that—even when told about the shortcoming of rifampicin compared with aminoglycoside—most patients preferred to use a convenient all-oral combination, although the risk of relapse is higher.⁸ Furthermore, even when doctors are aware of the superiority of the regimen containing aminoglycoside, most prescribe the convenient but inferior regimen.⁹ Convenience may lead to better adherence, and thus improved overall outcome, which may be crucial for a disease that requires many weeks of treatment.

The review also finds that longer durations of treatment (six weeks) significantly reduce relapses and treatment failure compared with shorter durations (less than 30 days). Rates of relapse could possibly be reduced further if regimens were continued for longer than six weeks.

Cure in brucellosis is defined purely on clinical grounds by the absence of symptoms and signs of residual or relapsing disease. In addition, the definition of chronic disease and its parameters are vague. Recent studies, however, have shown a residual bacterial load in a considerable proportion of clinically healthy patients who have had brucellosis, even one to three years after “cure.”¹⁰ If such a pathogenic process exists, in future we may have to redefine what is meant by treatment success or cure.

The need for a global collaboration to tackle the

medical, social, and political aspects of brucellosis has never been greater. The coalition of experts that was initiated in Ioannina, Greece, in 2006, which resulted in the “Ioannina recommendations,”¹¹ and the publication of research such as that by Skalsky and colleagues are paving the way forward. Global clinical trials recruiting thousands of patients and the development of a global *Brucella* database are currently under way.

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African sleeping sickness

Eflornithine should be the drug of choice for stage 2 disease, but resistance must be monitored

When human African trypanosomiasis (sleeping sickness) killed millions of people during Africa's colonial period 60-100 years ago, interest was similar to that for today's HIV epidemic, but the disease is now largely forgotten. The continuing importance of this disease is highlighted in the accompanying paper by Priotto and colleagues, who report the effectiveness and safety of eflornithine used for its first line treatment.¹

The most common form of human African trypanosomiasis is caused by the parasite *Trypanosoma brucei gambiense* and is transmitted by the tsetse fly.² Because diagnostic tests are too complex to integrate into primary health care, by the time most cases present they have already progressed from the benign easily treatable stage of the disease (haemolymphatic, stage 1) to the late stage (meningoencephalitic, stage 2), where parasites invade the central nervous system. If the disease is untreated, the patient has almost a 100% risk of dying within one to four years, after progressive neurological degeneration.

Only two drugs are available for treatment of late

stage disease. The first is a derivative of arsenic, melarsoprol. In areas where resistant parasites may be prevalent—such as Sudan, Uganda, the Democratic Republic of Congo, or Angola—melarsoprol has a cure rate of less than 70%.³ About 3-5% of patients die from drug induced encephalopathy.

The second treatment is α -difluoromethylornithine (DFMO, eflornithine).⁴ This drug, registered in 1990 for human African trypanosomiasis, was abandoned by Aventis in the late 1990s because of its lack of profitability, just as Bristol-Myers-Squibb launched an eflornithine based facial hair removal cream (Vaniqa). Fierce campaigning by the World Health Organization (WHO) and Médecins Sans Frontières (MSF) led Aventis to resume production in 2001. Sanofi-Aventis has made a commitment until 2011 to provide free kits containing the required two week supply of eflornithine plus expensive material for perfusions; this kit is to be distributed by WHO.

This secure availability has encouraged wider adoption of eflornithine over melarsoprol, with the risky assumption that it would be safer and no less effective. The assumption rested on evidence from

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about 1000 patients treated with various dosages and formulations who were mostly not followed up beyond 12 months—an insufficient amount of time to detect late relapses.⁵ In Priotto and colleagues' study—which follows up 1055 patients with stage 2 disease for cure rates, deaths, and adverse events during treatment—about 64% of people were followed up for at least one year and 50% for two years. The study supports the widespread use of eflornithine by demonstrating its effectiveness and safety, while highlighting the dangers of administration without supportive care.

Priotto and colleagues' study indirectly supports evidence of a lower case fatality rate (1-2%) with eflornithine than with melarsoprol. Surprisingly, no trial has directly compared the two drugs, but some evidence of superiority comes from programmes that used the two drugs sequentially,^{6 7} and fatality rates for melarsoprol are well documented and consistently higher than for eflornithine across various settings.

Severe adverse events (mainly seizures, fever >39.5°C, severe diarrhoea, and severe bacterial infections) were reported in 13% of patients. Although Priotto and colleagues used a retrospective record based assessment of adverse events, which could be hampered by under-reporting, these results are consistent with prospective observations of eflornithine and far lower than those from studies of melarsoprol. Bone marrow toxicity, a known effect of eflornithine not measured in Priotto and colleagues' study, may underlie many of the treatment emergent episodes of infection, and warrants further investigation. Most bacterial infections were successfully managed in this and other studies, but resource poor facilities that lack proper antibiotics, nursing care, and skilled clinicians could experience higher case fatality.

Effectiveness was moderately high (88% by survival analysis), but the occurrence of relapses in at least 7.6% (70/924) of patients is worrisome—patients who relapse have a high risk of death, and anecdotal evidence of treatment failure with eflornithine is accumulating. As with melarsoprol, relapse was associated with severity of illness on admission (eflornithine might not achieve minimum inhibitory concentrations in patients with high parasite density in their cerebrospinal fluid because of poor pharmacokinetic properties³) and male sex (reinfection in men with occupational exposure to tsetse bites might confound this association).

Although resistance is not necessarily the reason for treatment failure, resistance is readily induced in vitro and its emergence in the field would be disastrous.⁸ Combination treatment might help avert resistance and its transmission. Coadministration of eflornithine and nifurtimox (a drug registered for Chagas' disease and modestly effective as monotherapy for human African trypanosomiasis³) is being tested in a multicentric trial, and initial findings show excellent efficacy with equal or better

safety than either drug alone, possibly as a result of lower doses.^{9 10} Concerns exist, however, about nifurtimox's possible long term genotoxicity, which has been noted in some animal experiments.¹¹

Evidence so far supports the policy of eflornithine replacing melarsoprol as first line treatment of stage 2 disease, but a cautious eye must be kept on resistance. However, eflornithine's cost and cumbersome logistics of administration mean that new and better drugs are urgently needed. The highest level of investment in control since the colonial period has led to a reduction in transmission in most foci of human African trypanosomiasis after two decades of resurgence. This has prompted ambitious calls for elimination, which WHO is committed to spearheading.¹²

Research to develop new drugs and diagnostics for this disease is now supported by about \$100m (£50m; €67m), mostly from charities. Promising compounds for treatment of stage 2 disease are being explored—for example, by the Bill and Melinda Gates Foundation funded Consortium for Parasitic Drug Development and the Drugs for Neglected Diseases initiative.³

Meanwhile, a combination of eflornithine-nifurtimox could become the therapeutic mainstay by 2010. Advocacy for neglected tropical diseases often focuses on the lack of drugs but should not overlook simple epidemiological realities—earlier case detection through reinforced screening programmes is the best way to avoid the complications of treatment for stage 2 human African trypanosomiasis.

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New treatments for kidney cancer

New treatments offer hope, but await regulatory approval in the UK

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Renal cell cancer is a relatively unusual tumour. It accounts for less than 1% of deaths from malignant disease and is diagnosed in about 2500 people each year in the United Kingdom and 200 000 people worldwide.^{1 2} Our understanding of the molecular biology of renal cell cancer has recently undergone many changes. These changes have informed the development of drugs, and new treatments have become available. The most recent of these, the multitargeting kinase inhibitors, have improved the outlook of patients with renal cell cancer to such an extent that older treatments are becoming obsolete. However, despite evidence of their effectiveness their availability in the UK has lagged behind that in the United States because of the time taken to obtain regulatory approval. So what is the evidence of the effectiveness of these treatments?

The clue to the molecular changes involved in renal cell cancer come from the Von Hippel Lindau syndrome, in which a mutation in a tumour suppressor gene at chromosome 3p results in an inherited form of renal cell cancer. This mutation leads to the accumulation of hypoxia inducible factors, α and β . This in turn causes upregulation of growth factors, including vascular endothelial growth factor and platelet derived growth factor, which are thought to drive the growth of renal cell cancer.³ New treatments are aimed at the downregulation of such growth factors.

One of these treatments is bevacizumab, which is a humanised neutralising antibody against vascular endothelial growth factor. Efficacy in renal cell cancer was first shown in a randomised controlled trial of 116 patients with metastatic renal cell cancer, where the time to progression was significantly reduced in people taking bevacizumab compared with placebo (4.8 months *v* 2.5 months; $P < 0.001$).⁴ Renal cell cancers also express other cell surface receptors, including receptors for epidermal growth factor (EGFR) and Herceptin (cerbB-2).^{5 6} In one uncontrolled phase II study investigating the possibility of a synergistic effect between multiple receptor regulation, bevacizumab was combined with erlotinib—a tyrosine kinase inhibitor of EGFR. Of 59 assessable patients 15 responded to treatment as measured by the response evaluation criteria in solid tumors (RECIST) criteria. These responses were maintained such that after a median follow-up of 15 months, median survival had increased. Although toxicity was frequent, it was not severe and was acceptable to patients.⁷ In a randomised controlled trial lapatinib—an orally active tyrosine kinase inhibitor of cerbB-2 and EGFR—was compared with hormonal therapy in 417 patients. In the 241 patients overexpressing EGFR (who might be expected to respond because of the molecular characteristics of their tumour), the median overall survival was 46 weeks compared with 38 weeks for patients treated with hormonal therapy ($P = 0.02$).⁸

Temsirolimus is an inhibitor of angiogenesis and of mTOR (mammalian target of rapamycin) kinase—a com-

ponent of intracellular signalling pathways involved in cell growth and proliferation.⁹ A randomised controlled trial of 626 patients with kidney cancer compared temsirolimus, interferon, or both agents. The median overall survival of patients taking temsirolimus was significantly higher than those taking interferon or the combination (10.9 months *v* 7.3 months *v* 8.4 months; $P = 0.008$). Side effects were minor.¹⁰

Two recent randomised controlled trials have provided even more hope for patients with renal cancer. The first compared sorafenib—an inhibitor of EGFR and other growth factors and their receptors—with placebo in 903 patients. Median progression-free survival was significantly higher in patients taking sorafenib than in those taking placebo (5.5 months *v* 2.8 months; $P < 0.01$).¹¹ The second trial compared another multitargeting agent, sunitinib, with interferon alfa in 750 patients. The median progression-free survival was significantly higher in people taking sunitinib (11 months *v* 5 months $P < 0.001$). Objective responses were seen in 103 of 335 (31%) of the sunitinib group and in 20 of 327 (6%) of the interferon group ($P < 0.001$). Toxicity and quality of life were significantly better in the sunitinib group.¹² In addition, and perhaps more importantly, the rate of disease stabilisation and lack of progression was double that of the interferon arm. This has led to the treatment of renal cell cancer being assessed differently, with response not being the ultimate and only goal. On the basis of these findings, patients and their doctors have welcomed these agents as a major advance in the treatment of renal cell cancer. Current trials are exploring the possibility of combining these multitargeting tyrosine kinase inhibitors and using them with cytokines.

Potentially there is real hope for patients with kidney cancer, but when will hope translate into the reality of treatment being available in the UK? Sunitinib was approved by the Food and Drug Administration in the US in January 2007, in the same month that the trials were published. Sunitinib and sorafenib were licensed by the European Medicines Agency in July 2006. Patients in the UK should not have to wait for another two years pending the National Institute for Health and Clinical Excellence to approve the use of multitargeting kinase inhibitors in kidney cancer.

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Health of the working age population

New report recommends integration of occupational health into mainstream health care

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On 17 March 2008, Dame Carol Black launched her review of the health of the United Kingdom's working age population, "Working for a Healthier Tomorrow."¹ Importantly, the review was presented to the secretary of state for work and pensions as well as the secretary of state for health. Dame Carol's position as national director for health and work straddles the two departments that, along with the Health and Safety Executive (sponsored by the Department of Work and Pensions), have been working together since 2005 on a health, work, and wellbeing agenda.²

The review was informed by a "call for evidence," which produced more than 260 written responses from various organisations including occupational health organisations, patient groups, employers, local councils, trades unions, and even the "big lottery fund."

The review is reminiscent of the report published by Dame Carol's predecessor as president of the Royal College of Physicians, Sir Douglas Black, in 1980.³ That report, which the government of the day tried to suppress, examined inequalities in health. This new Black review examines a similar failure of health and social policy in a neglected section of the British population—people of working age.

Welfare payments cost £30bn (€38.6bn; \$59.4bn) each year in people of working age, and incapacity benefits given to 2.5 million people make up 36% of this cost. Much of the descriptive part of the review covers incapacity to work as a result of ill health. Many people with health conditions or long term disabilities can work and want to work, but they are dissuaded from doing so by societal expectations and sometimes by overprotective doctors. The truism that work is good for you has only recently been evaluated in detail.⁴ Getting sick employees back to work as soon as possible is not just of economic benefit to the government—it is a positive health promoting measure for patients that all doctors should adopt.

So why has the problem not been sorted out before in a country with a National Health Service and a well developed benefits system? The review cites many reasons: in contrast to many European countries, occupational health services were not incorporated into the NHS at inception; there are often long delays in investigating non-serious but work limiting conditions (such as shoulder pain); back pain and mild to moderate mental health conditions are excessively medicalised and often wrongly attributed to work; the "sick note" system is an

unaudited farce misused by doctors and patients alike; employment law in relation to ill health is complex; and benefit payments can provide perverse incentives to stay out of work.

So what solutions does the review provide? The main measure, unfortunately announced in isolation before the publication of the review, was that sick notes should be replaced by "fit notes." This idea has proved unpopular with general practitioners, who see themselves primarily as patient advocates.

Comprehensive occupational health services are accessible to only 3% of the working population in the UK, so general practitioners are key to improving the medical management of people both in and out of work. The review recommends the mainstreaming of occupational health into the UK's healthcare system. Rather than going for a full blown national service framework for health impairment in relation to work, Dame Carol prescribes a "case-managed multidisciplinary Fit-for-Work service based on the bio-psychosocial model which would ensure a prompt, holistic assessment of patient's needs and provide them with an individualised action plan for achieving recovery." This case management approach has face validity, but so far the results of trials have been mixed,⁵ and it is labour intensive and expensive. It will need to be run by highly trained and sensitive people, and it is vulnerable to being criticised by cynics who detect economic rather than health promoting imperatives. Electronic fit notes and a "fit for work" service are two of 10 practical recommendations that urgently need to be piloted.

Solutions are difficult because of entrenched social attitudes (which deride the sick note or benefits culture), and the UK has not utilised the skills of occupational health or rehabilitation professionals in the same positive way as some other countries, such as those in Scandinavia.

Dame Carol makes a good case for rejecting the status quo, and that money must be spent to save money. Her suggestions will require real investment—mainly government investment in making occupational health support available much more widely and the involvement of more people across a range of disciplines. Will the government, employers, and our patients trust one another and give these initiatives a chance? A consensus statement in the review (p 67) suggests that the healthcare community is ready to go.¹

All references are on bmj.com