Animals in research: "can they suffer?"

Home Office figures showing a rise in the number of animal experiments in the UK in 2010 should be of interest to all involved in medical research and treatment. Even *The Lancet*, whose primary concern is clinical research, must attend to them. Many of the advances published in these pages have their origins in animal models; furthermore, it is the duty of all involved in medical research to ensure that this research is undertaken, in every area, within a clear ethical framework. Whether animals have "rights" or not, we must not forget the responsibilities we hold both towards them and towards the patients whose treatments are informed by the experimental process.

Many hope that in the long term the advance of biotechnology will eliminate the use of animals in research. In the short term, it is likely to present us with new and troubling ethical questions. These are bravely addressed in a new report from the Academy of Medical Sciences, *Animals Containing Human Material*. The report defines "animals containing human material" (ACHM) as animal entities that have either had their DNA sequences modified to resemble those found in human beings, or animals that have human cells incorporated into them. This technology, which can improve the congruence between the animal model and its human counterpart, is widely used when computer models or cell cultures do not provide sufficient accuracy, or when human experiments would be unethical. Yet there has been little dialogue on the subject between scientists and the public.

If researchers have been reluctant to engage with the public for fear of provoking a negative response, the ACHM report suggests that these worries have been ill-founded. A public dialogue undertaken by Ipsos MORI as part of the study showed that people would accept ACHM research that was well regulated and could be justified in terms of benefit to medical progress. Participants, the report states, "did not regard ACHM research as being significantly different from other research involving animals". The most common reason why ACHM was thought unacceptable was not religious or philosophical in nature: it was simply concern about animal welfare.

The report also looks ahead to types of experiment that might arise in the future. For example, it is feasible that one day research might be proposed involving the creation of animals modified to display distinctly human-like features or characteristics; if this process extended to neural tissue, one might imagine creatures with human cognitive processes or patterns of behaviour. Whether or not this comes to pass, it does not substantially alter the core issue raised by philosopher Jeremy Bentham over 200 years ago regarding the treatment of animals: "the question is not, can they reason? Nor, can they talk? But, can they suffer?"

The report's recommendations are therefore welcome, in as much as they promise to minimise suffering, to promote high-quality research, and to open an inclusive and ongoing conversation about ACHM. It is proposed that the Home Office should establish a national expert body to provide specific guidance on ACHM use in research. The level of regulation would depend on which of three proposed divisions the research falls into: experiments that present no issues beyond the ordinary use of animals; those that should be restricted subject to scrutiny; and those that should not be undertaken pending further understanding of the potential consequences.

There is a lesson in this approach for all those who are concerned about animal use in medical research, on both sides of the debate. Those who advocate its benefits must endeavour to keep their own house in order. Publication of data in *PLoS One* in 2009, suggesting a low level of quality in the design and reporting of many animal experiments rightly alarmed many, and there is simply no other solution than for researchers, funders, and publishers to demand transparency and the highest possible scientific and ethical standards, as set out in the ARRIVE guidelines. It is clear, however, that this cannot be done in an atmosphere of fear and intimidation. It is doubtful whether those who hold the belief that all animal experimentation is an absolute moral wrong will change their minds; yet they would do well to consider that mutual respect and an open channel for dialogue could do much to further their aims. The use of animals in medical research is a practical and ethical issue that will not go away—nor should it. Only through a constant, dynamic process of scientific and moral scrutiny can one be sure that the correct balance—however fine, however tentative—is being struck.

■ *The Lancet*

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For the **Home Office figures on animal research** see http://www.homeoffice.gov.uk/publications/science-research-statistics/research-statistics/science-research/spanimals10/

For the **Academy of Medical Sciences report** see http://www.acmedsci.ac.uk/publications

For the ***PLoS* paper on the quality of animal experiments** see http://www.plosone.org/article/info:doi/10.1371/journal.pone.0007824

For the **ARRIVE guidelines for reporting animal research** see http://www.nc3rs.org.uk/page.asp?id=1357

The long road to improvement of human rights in China

Sipa Press/Rex Features

For the **National Human Rights Action Plan (2009–2010)** see http://www.dhnet.org.br/dados/pp/nacionais/pndh_china_2009_2010_a.pdf

For the **Chinese Government's assessment of the plan** see http://www.chinadaily.com.cn/china/2011-07/14/content_12903577.htm

For the **Human Rights Watch report** see http://www.hrw.org/en/reports/2011/01/11/promises-unfulfilled

"China fulfills all targets of its Human Rights Action Plan", read the headline from *Xinhua*—China's official state media—on July 14, reporting the government's assessment of its National Human Rights Action Plan (2009–2010). It was a claim that few observers could believe.

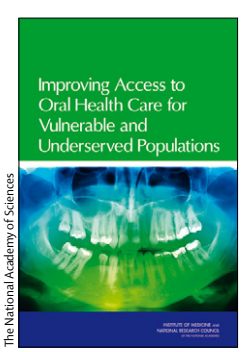
In April, 2009, the Chinese Government launched its much-needed plan to improve human rights in the country. The plan covered several areas for improvement, including the right to a fair trial, rights of detainees, the right to health, the right to basic living conditions, and women and children's rights. It called for some concrete measures such as expansion of social insurance, regular health check-ups for people older than 65 years, and interrogation rooms with physical separation between interrogators and detainees to prevent torture. The relevant government departments were expected to implement the plan.

However, although good in principle, the plan lacked meaningful benchmarks, omitted mention of the rights of lesbian, gay, and transgender people, and failed to appoint an independent body to evaluate the plan's progress. These flaws make it hard to assess what has actually been achieved. Moving forward, a new human rights plan needs to address these issues and tackle the serious infringement of people's rights in China today.

Human Rights Watch accurately detailed the situation in their assessment of China's plan, entitled *Promises Unfulfilled*, released in January this year. Although the report notes that some progress has been made (eg, health reform that has provided millions of citizens with basic health insurance and repeal of a travel ban on HIV-positive foreign visitors), it draws attention to many human-rights violations. For example, at present, around 500 000 suspected drug users are being held in mandatory drug detention centres, and abuse of detainee rights remains common, as does discrimination against people who have HIV/AIDS and harassment of individuals and groups that defend the rights of people with HIV/AIDS.

China's National Human Rights Action Plan admitted that the country "has a long road ahead in its efforts to improve its human rights situation". 2 years on, progress along that road has been slow and uneven. ■ *The Lancet*

Oral health care in the USA



The National Academy of Sciences

For the **Institute of Medicine report** see http://www.iom.edu/Reports/2011/Improving-Access-to-Oral-Health-Care-for-Vulnerable-and-Underserved-Populations.aspx

On July 13, the US Institute of Medicine released *Improving Access to Oral Health Care for Vulnerable and Underserved Populations*, which outlines solutions to reduce the existing oral health-care disparities in groups such as children, seniors, ethnic minorities, and rural populations.

An estimated 33·3 million Americans lack access to basic oral health care. Government-funded health programmes, primarily serving vulnerable populations, do not cover dental health care in adults. As a result, 62% of US retirees in 2006 did not have dental coverage. By law, children in the USA have dental health coverage from state-run public programmes. But, even then, an estimated 4·6 million children in 2008 did not receive dental care.

The report recommends integration of oral health care into overall health care. Poor oral health is associated with increased emergency service use, and an increased risk of diabetes and respiratory and heart diseases. Health-care professionals (such as nurses and physician assistants) can be used to screen for oral disease and deliver preventive services.

Existing regulations on how oral health care is delivered in the USA must also be amended. State legislation does not take advantage of the full extent of oral health professionals' education and training. For example, the report mentions that 22 US states unnecessarily require a dentist to examine a child before a dental hygienist can apply the sealant that prevents cavities.

Training of an increased number of dental health professionals is also needed. Currently there is a shortfall of 9900 dentists in the USA. The report recommends that under-represented minorities are recruited into dental education programmes and that community oral care (treatment of diverse populations in a different setting) should be an educational requirement.

Oral health remains an indicator of health disparity in the USA, 10 years after the US Surgeon General brought the topic to the attention of the nation. Implementation of federal, state, local, and community efforts are overdue to endorse the fact that good health is not possible without good oral health. ■ *The Lancet*

Arresting type 1 diabetes after diagnosis: GAD is not enough

Published Online June 27, 2011 DOI:10.1016/S0140-6736(11)60978-1

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That administration of glutamic acid decarboxylase formulated with aluminium hydroxide (GAD-alum) does not arrest C-peptide decline in patients with recent-onset type 1 diabetes is the main message of an Article by Diane Wherrett and colleagues in *The Lancet*.[1] In a trial comprising 145 patients recently diagnosed with type 1 diabetes, two or three doses of GAD-alum immunotherapy did not alter the disease course as judged by the primary endpoint, geometric mean area under the curve of serum C-peptide during a mixed meal tolerance test at 1 year. After a negative study aimed at arresting the immune destruction of β cells in such patients, the inclination might be to abandon hope for prevention of type 1 diabetes. However, we believe this study is an important step in research towards future interventions for type 1 diabetes.

First, Wherrett and colleagues' study[1] is an example of how concepts should be tested: after years of organisation and with financial support from many stakeholders, Type 1 Diabetes TrialNet[2] is a highly efficient group, able to move from idea to protocol, recruitment, and results in months. This rapid approach is the way forward, with motivated clinical researchers, networks linking all participating centres to academic centres, and an efficient back office. Worldwide, several consortia have shown that this approach allows for rapid, reliable testing of hypotheses.[3,4] The challenge will lie in how to select interventions. Again, TrialNet has come up with an efficient concept: democracy with guidance. Ideas can be presented to the consortium, and when TrialNet members are convinced by the preclinical and pilot clinical data, a working group is composed and charged with investigating the feasibility of a trial and writing the protocol. This working group then leads the trial.

Second, Wherrett and colleagues' study shows that by doing a trial well, one can quickly confirm or refute hypotheses. A thorough power calculation and, in particular, clinically relevant endpoints are essential. These endpoints should, at the stage of the disease being investigated, be measures of residual endogenous insulin secretion, preferably through dynamic testing because measuring C-peptide during fasting or at random times will not show the small increments in function or mass that might be achieved. In our trial[4] with anti-CD3, we used the hyperglycaemic clamp—the gold standard for measurement of functional β-cell mass—but this test is cumbersome and cannot be done in all centres.[4,5] The mixed meal tolerance test[6] used by Wherrett and colleagues[1] is well established and standardised to allow reliable conclusions about stimulated C-peptide secretion in large multicentre trials (table). Readouts, such as HbA_{1c} or rate of hypoglycaemia, that agencies might like (owing to their experience in pharma-driven trials on new agents) are not helpful in patients with recent-onset, C-peptide-positive type 1 diabetes.

Finally, perhaps the most important conclusion from this study is not to ignore the published work in

	Action	Patients			Stimulation test	Reported outcome on C-peptide secretion *vs* placebo	Reference
		n	Age (years)	Diabetes onset (weeks)			
Otelixizumab	Anti-CD3	80	12–39	<4	Clamp	Higher stimulated C-peptide	4
Rituximab	Anti-CD20	78	8–40	<13	MMTT	Higher stimulated C-peptide	7
Etanercept	TNF-inhibitor	18	3–18	<4	MMTT	Higher stimulated C-peptide	8
Mycophenolate mofetil ± daclizumab	General IS ± anti IL2	126	8–45	<13	MMTT	No difference	9
Teplizumab	Anti-CD3	544	8–35	<12	MMTT	Await reporting	..
Otelixizumab	Anti-CD3	272	12–45	<13	MMTT	No difference	10

CLAMP=hyperglycaemic clamp test. MMTT=mixed meal tolerance test. TNF=tumour necrosis factor. IS=immune suppression. IL=interleukin.

Table: **Double-blind randomised controlled trials investigating the effect of immunotherapy on stimulated C-peptide in recent-onset type 1 diabetes**

non-obese diabetic mice, a model of type 1 diabetes. This research has been dismissed as irrelevant because the disease induced is too artificial and, in particular, too easy to prevent.[11] However, published reports show that many interventions fail to prevent diabetes in non-obese diabetic mice or that mistakes are made in translation of the findings to humans.[12] For example, for GAD: timing of administration (works best early in life, before disease sets in), dose (given that a mouse weighs 20 g), method of administration (eg, oral, inhaled, DNA vaccination), peptide length (intact GAD or short peptides), and in particular the vehicle for GAD (with or without adjuvant) all have a role and yield very different results in non-obese diabetic mice.[13] Of note, use of GAD-alum has never been reported in non-obese diabetic mice.

So, what does the non-obese diabetic mouse model really tell us? Prevention in genetically at-risk mice—when autoimmune attack has not yet started—is straightforward and can be done by many interventions, including diet (eg, vitamin D, exclusion of cow's milk). However, once autoimmunity starts, stopping diabetes becomes difficult and immune modulation involving reprogramming of T lymphocytes is necessary. Research in the non-obese diabetic mouse points to anti-CD3 antibodies, until now also the intervention yielding the best results after onset of diabetes in patients.[14] However, in non-obese diabetic mice, timing of administration and a high dose of anti-CD3 are crucial, points which should be considered in analysis of human intervention trials of anti-CD3. But still, after the immune system is reset, antigen-specific reprogramming will be needed. The aim is not to induce tolerance to everything, but only to the β cell. Most experts agree that combination therapy will be the solution, with combinations of immune modulating drugs or interventions (possibly including anti-CD3) at lower doses and an antigen-specific approach—why not GAD?[15]

Researchers should not give up hope of preventing or curing type 1 diabetes. The machinery exists to do the trials, as do the ideas and motivation. What is needed is the continued interest of agencies, pharmaceutical companies, and the scientific community in the quest to beat this disease.

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We declare that we have no conflicts of interest.

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