

component of ethical review, and ensure that patients are advised to withhold their consent to participate unless there is publicly accessible information about the trial and the investigators have undertaken to make the results of the study publicly available within a reasonable time after its conclusion.

GA and IC have worked for registration of controlled trials over many years because this is a responsibility of our salaried positions. We have advised the European Science Foundation, Current Controlled Trials, and other organisations, in Germany, the UK, and other countries, but we have not received fees for this advice. Current Controlled Trials has offered to make a contribution to a research charity chosen by Iain Chalmers when he retires and steps down as chair of its international advisory committee at the end of June.

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- 1 Goldbeck-Wood S. Denmark takes lead on research ethics. *BMJ* 1998; **316**: 1189.
- 2 Mann H. Research ethics committees and public dissemination of clinical trial results. *Lancet* 2002; **360**: 406–08.
- 3 Dickersin K. How important is publication bias? A synthesis of available data. *AIDS Educ Prev* 1997; **9** (suppl 1): 15–21.
- 4 Egger M, Jüni P, Bartlett C, Hoenstein F, Sterne J. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. *Health Technol Assess* 2003; **7**: no 1.
- 5 Chalmers I. Using systematic reviews and registers of ongoing trials for scientific and ethical trial design, monitoring, and reporting. In: Egger M, Davey Smith G, Altman D, eds. *Systematic reviews in health care: meta-analysis in context*, 2nd edn. London: BMJ Books, 2001: 429–43.
- 6 Lock S, Wells F. Preface to the second edition. In: Lock S, Wells F, eds. *Fraud and misconduct in medical research*. London: BMJ Publishing Group, 1996: xi–xii.
- 7 Chalmers I. Lessons for research ethics committees. *Lancet* 2002; **359**: 174.
- 8 Savulescu J, Chalmers I, Blunt J. Are research ethics committees behaving unethically? Some suggestions for improving performance and accountability. *BMJ* 1996; **313**: 1390–93.
- 9 Tonks A. A clinical trials register for Europe: stop talking and start making it happen. *BMJ* 2002; **325**: 1314–15.
- 10 Simes RJ. Publication bias: the case for an international registry of clinical trials. *J Clin Oncol* 1986; **4**: 1529–41.
- 11 TrialsCentral. Your source for online clinical trials information. <http://www.trialscentral.org> (accessed Feb 19, 2003).
- 12 ClinicalTrials.gov. Linking patients to medical research. <http://www.clinicaltrials.gov> (accessed Feb 19, 2003).
- 13 Current Controlled Trials. Featuring the metaRegister of controlled trials. <http://www.controlled-trials.com> (accessed Feb 19, 2003).
- 14 European Science Foundation Policy Briefing. Controlled clinical trials. No 13, May, 2001: <http://www.esf.org/publication/90/ESP13.pdf> (accessed Feb 17, 2003).
- 15 European Science Foundation. Press release on registration of randomised controlled trials: for attention and action by Chief Executives, ESF Member Organisations. Feb 11, 2003: <http://www.esf.org> (accessed Feb 17, 2003).
- 16 Manheimer E, Anderson D. Survey of public information about ongoing clinical trials funded by industry: evaluation of completeness and accessibility. *BMJ* 1996; **325**: 528–31.
- 17 Sykes R. Being a modern pharmaceutical company. *BMJ* 1998; **317**: 1172.

Taking the sting out of ant stings: venom immunotherapy to prevent anaphylaxis

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Ants (Formicidae), like bees, wasps, and hornets, are insects of the order Hymenoptera. Usually they threaten human beings only by their prodigious numbers and ruthless, organised, and persistent pervasiveness. In Australia, the first recorded envenoming by an endemic animal did not involve any of that country's formidable snakes, spiders, or cnidarians but a mass attack by green

tree-ants (*Oecophylla smaragdina*) on the pioneering naturalist Joseph Banks, in 1770.¹ However, the bite of even a single ant can be traumatic, as in the case of the giant *Paraponera gigantea* (“tocandira”) of Rondonia, Brazil, which is 22 mm long. One sting by some species of ant may provoke fatal anaphylaxis in a sensitised person.

Anaphylaxis is increasingly recognised as an important mode of death in many parts of the world. Apart from drugs and foods, stings by Hymenoptera are among the most familiar precipitants. In England, wasps and hornets (Vespidae) and bees (Apidae) are responsible for four to five of the average of about 20 deaths attributed to anaphylaxis each year, although some cases are probably missed. The USA has a similar pattern among a total of perhaps 50–60 anaphylactic deaths each year. However, between 1920 and 1940, two species of fire ants (*Solenopsis richteri* and *S. invicta*) were inadvertently imported from South America. The distribution of *S. richteri* has remained relatively restricted around its original port of entry at Mobile, Alabama, whereas *S. invicta*, “the ant from hell”, has spread throughout south-eastern USA. Between 0.8% and 40% of Americans are now thought to be hypersensitive to venom from these ants, and more than 50 anaphylactic deaths from the sting of imported fire-ants have been reported since 1972.² In some parts of Australia, ant-sting anaphylaxis has now emerged as an important medical problem, but there it is caused by indigenous rather than imported ants. Of the three species commonly involved, *Myrmecia pilosula* (the “jack-jumper”), has proved the most dangerous. The name refers to its saltatory style of locomotion when disturbed. The jack-jumper inhabits Perth, south-eastern Australia from the Eyre Peninsula to Rockhampton, and especially the island of Tasmania. The increase in numbers of these ants has been blamed on the proliferation of human dwellings and the decline of the ant's major predator, the echidna.

Clarke³ first publicised the increasing problem of anaphylaxis from the sting of *M. pilosula* in Tasmania in 1986. More recently, at the Royal Hobart Hospital Emergency Department, 21–25% of the 324 cases of anaphylaxis treated with epinephrine between 1990 and 1998 were attributable to *M. pilosula* stings, compared with only 13% caused by honeybee stings. Between 1980 and 1999, four deaths occurred in a population of 223 000.⁴ Undoubtedly, the prompt use of self-injectable epinephrine could prevent most cases of severe anaphylaxis, but desensitisation offers even greater insurance against sting reactions. In people who had had anaphylactic reactions to bee and wasp stings, desensitisation, by injection of a series of increasing doses of the appropriate hymenopteran venom, was first validated in 1978.⁵ The mechanism of desensitisation remains uncertain but earlier notions of an induction of IgG “blocking” antibody have yielded to evidence that, in hypersensitive individuals, immunotherapy causes a switching of the abnormal Th2 cytokine response (interleukins 4 and 13), which stimulates secretion of IgE by B cells, to Th1 responses (interleukin 2 and interferon gamma), which block this production.⁶

The effectiveness of venom immunotherapy against hymenoptera-sting anaphylaxis is supported by clinical experience,⁷ but the most impressive evidence so far that this therapy can prevent severe life-threatening anaphylaxis is now provided by the investigation of jack-jumper stings in Tasmania, reported by Simon Brown and colleagues in today's *Lancet*. The rigorous protocol of this double-blind placebo-controlled crossover trial was demanding both on its 68 highly-motivated and

courageous participants, who risked another experience of anaphylaxis, and on the investigators, who risked provoking these life-threatening events through sting challenge. The uncompromising design is justified by the investigators. Only their decision to delay epinephrine treatment in those who developed systemic reactions, until progression to "significant" respiratory or cardiovascular compromise (or until the patient asked for relief of their symptoms), might be regarded as controversial. The results are thoroughly convincing. Desensitised patients were protected against severe sting-induced anaphylaxis, whereas the risk of such reactions in patients who were not desensitised exceeded 70%. This prophylaxis can be recommended for susceptible patients in Australia. It will require a sustained supply of *M pilosula* and, perhaps, some other ant venoms.

Between 1989 and 1994, soon after the problem of jack-jumper stings was first recognised, the late Struan Sutherland of the Commonwealth Serum Laboratories (CSL) was awarded Federal Government funding to collect the venom of *Myrmecia* ants for desensitisation purposes.⁸ That initiative eventually failed through technical problems with standardisation of venom and underfunding by CSL.⁹ However, the demonstration by Brown and colleagues of such impressive evidence of the efficacy of immunotherapy with jack-jumper ant venom now justifies more research investment in this area.

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- 1 Southcott RV. Some harmful Australian insects. *Med J Aust* 1988; **149**: 656–62.
- 2 Prahlow JA, Barnard JJ. Fatal anaphylaxis due to fire ant stings. *Am J Forensic Med Pathol* 1998; **19**: 137–42.
- 3 Clarke PS. The natural history of sensitivity to jack jumper ants (*Myrmecia pilosula*) in Tasmania. *Med J Aust* 1986; **145**: 564–66.
- 4 Brown SGA, Wu Q-X, Kelsall GRH, et al. Fatal anaphylaxis following jack-jumper ant sting in southern Tasmania. *Med J Aust* 2001; **175**: 644–47.
- 5 Hunt KJ, Valentine MD, Sobotka AK, et al. A controlled trial of immunotherapy in insect hypersensitivity. *N Engl J Med* 1978; **299**: 157–61.
- 6 McHugh FM, Deighton J, Stewart AG, et al. Bee venom immunotherapy induces a shift in cytokine response from a TH-2 to a TH-1 dominant pattern: comparison of rush and conventional immunotherapy. *Clin Exp Allergy* 1995; **25**: 828–38.
- 7 Mueller ER. Insect sting allergy: clinical picture, diagnosis and treatment. New York: Gustav Fischer, 1990.
- 8 Sutherland SK, Tibballs J. Australian animal toxins: the creatures, their toxins and care of the poisoned patient, 2nd edn. Melbourne: Oxford University Press, 2001.
- 9 Sutherland SK. A venomous life. Melbourne: Hyland House, 1998: 313–17.

Catastrophic burns in children: prediction of mortality

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Marcus Spies and colleagues' report in today's *Lancet* is yet another from the Galveston Shriners Hospitals that shows their ability to lead the world in paediatric burn care. Their burn-survival figures are second to none and a standard which all should seek to attain. In this analytical study Spies and colleagues have developed an accurate mathematical model and predictor of outcome after serious burn injury, which shows that a decision to cease resuscitation cannot be taken at admission but only after reassessment and review of vital signs and biochemistry over a few weeks. Patients with massive burn injuries often survive at the Galveston

Shriners Hospitals and this study is accurate and informative. It should be noted that their burn population, their surgical approach, the high standard of team care offered including specialist burn surgeons, and their holistic approach to aftercare is different from that offered within the UK.

The current basis for a decision on whether to attempt the resuscitation of burned patients on most units in the UK is based on burn size, presence of significant inhalation injury, age of patient, and to some extent the involvement of anatomically important zones.¹ Recent feedback from burn survivors, however, has indicated that this process may not be entirely adequate, which is borne out by previous reports from the Galveston Shriners² where children surviving after massive burn injuries can adapt and integrate into society. Clearly, comparisons of burn-care standards between burn units cannot be made on survival alone and there are many other important standards of care that should be scrutinised, including quality-of-life outcome. Spies and colleagues' report becomes important, therefore, if it is considered that it is possible to accurately predict survival in badly burned children and understand that there can be a quality of life if appropriate support can be provided. Use of a model for prediction of fatal outcome after a long period of resuscitation will become an ethical and legal dilemma when a decision about the futility of further treatment has to be made.

One of the UK's leading burns units has indicated little progress over the past few decades.³ Such pessimism has not been the experience of other units although objective evidence cannot be provided because there are no working models to monitor outcome. Good inpatient care depends on the retention of high-quality staff, their motivation, and managerial support. There is a distinct and often forgotten need to audit, measure, evaluate, and research the care that burns units provide and management protocols need to be changed according to findings. If not, only a reasonable level of care will be maintained, rather than trying to reach the Galveston standard.

Burn-care outcomes other than survival or duration of inpatient stay cannot be easily measured but there is an urgent need for all burn units to provide standards of care and outcome data as the desire to establish centres of excellence gains momentum. The national burn-care review was finally published in 2001,⁴ and although it is based on inaccurate and incomplete data collection, it acts as an important foundation for the future and there are several issues that need to be addressed urgently. The provision of a few specialised centres for paediatric burns has to be a priority—the decision as to which, if any, of the current UK units should be allocated this prestigious role is vitally important since appropriate care for burns is extremely expensive. The choice will be a hard-fought contest and bids from burn units should be independently evaluated by a group that includes a specialist within the field of burn care. The decision will thus be independent and evidence-based before allocating an upgrade to burn-centre status. The right clinicians need to be at the right centres with the right staffing levels, and be able to provide the total burn-care package that is provided in Galveston.

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- 1 Slatore R, Frame JD. Management of burn injuries in children. *Eur J Plast Surg* 1996; **19**: 207–12.
- 2 Blakeney P, Meyer W, Robert R, Desai M, Wolf S, Herndon D. Long term psychological adaption of children who survive burns involving 80% or greater total body surface area. *J Trauma* 1998; **44**: 625–34.