non-obese groups. Such imbalance is unavoidable in this type of study, but we used multivariate analyses to correct for confounding factors.3 Contrary to their statement, the imbalance between the two groups did not affect the results, since obesity was not an independent risk factor in our multivariate analyses. Slim and colleagues also question the statistical power of our analyses. We agree that the study would be too small to detect a difference of 20%. However, we calculated a statistical power of 80%, assuming a reduction of 40% in morbidity (15% in non-obese patients and 25% in obese patients). Slim and colleagues also raise the issue of whether surgeons’ performance could be a confounding factor. We did not, however, assess this issue in our study.

At our centre, a staff surgeon is present in every case. R McCarthy and co-workers point out the limitations of a non-randomised and observational methodology. According to criteria of evidence-based medicine, our study ranks as a level 2, which presently provides the best evidence to identify outcome data in this population. A randomised study—ie, surgery in obese patients versus surgery in obese patients after weight loss—is hardly feasible taking into account that losing weight in obese patients is rarely successful. McCarthy and co-workers propose POSSUM as a comparative audit tool. The POSSUM scoring system has mainly been validated for hospital mortality rather than morbidity. Moreover, the POSSUM score includes intraoperative variables, such as intraoperative bleeding, which are typically biased by factors relating to the surgeon.4 Another difficulty with the POSSUM system is the need for preoperative examinations that are not routinely done in many procedures.5 McCarthy and co-workers’ statement that diabetes and cardiac diseases are independent risk factors is not supported by our multivariate analyses.

Finally, they claim that outcome data gathered during the hospital stay are inadequate. Although we agree that for a comprehensive assessment of surgical complications, such as incisional hernia, longer follow-up would be needed, the hospital stay during the study period ranged from 6 to 16 days (median) depending on surgical type. Therefore, we believe that the data presented are valid.


CORRESPONDENCE

Questions about comparative genomics of SARS coronavirus isolates

Sir—Yijun Ruan and colleagues’ analysis (May 24, p 1779)1 of the comparative genomics of coronavirus isolates from 14 patients with severe acute respiratory syndrome (SARS) is to be welcomed. Two questions, however, are begged by their survey.

The first question concerns genomic evolution of the SARS virus. The single-stranded RNA genome of the SARS virus assures genetic lability under moderate selective pressures and high rates of genetic drift. Droplets of respiratory-tract fluids in nasopharyngeal aerosols have volumes of 10–2–10–3 mL, so that the expected SARS virion population in a single droplet is between 0·1 and 10, even for patients with maximum degrees of viremia. Thus, most infective doses are probably in the range of 10–105 virions, whereas a patient’s SARS virion-load at peak viraemia is about 1016. Considering the 104 second effective serum lifetime of a virion, a single-cycle, or about 20 infective doses. Even with 103 successfully infective virions sourced per infected cell—a conservative upper-estimate—are there enough viral generations per case history, or about 20 viral generations across the three case-history generations studied by Ruan and colleagues. Since the observed per-base replication error-rate of RNA polymerases is about 3·10–3 and the SARS viral genome has about 30 000 bases, the expected genome copying error-rate is about one base per viral generation, or about 20 base errors of aggregate genetic drift after 20 generations, roughly congruent with the 16 “observed twice” single nucleotide polymorphisms reported by Ruan and colleagues.

Crucially, however, these 14 case-isolates represent infections during March and early April, 2003, whereas Ruan and colleagues relate that the SARS epidemic began in Guangdong province in November, 2002, so that it has been propagating and mutating at least four—and perhaps as much as five—times longer than is represented by the time-span of all the analysed cases. Where is the four-fold larger genetic drift? Specifically, why is there such close genomic similarity between the Singapore cases and all of the overseas cases? Unless these all trace to the same index case in early March, which seems unlikely, their close genomic similarity is quantitatively inexplicable.

The second question concerns the ease with which the SARS virus propagates in vitro, a quite unusual, if not unique, characteristic for known human coronaviruses. This issue is at best thoroughly puzzling and at worst deeply troubling. How do Ruan and colleagues think that this set of viral propagation peculiarities arose?

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Author’s reply

Sir—Lowell Wood raises concerns about our analysis of SARS coronavirus (SARS-CoV) strains, questioning the small number of mutations described. Although Wood is correct in his theoretical calculations, which are based on generalised in-vitro experiments, three explanations can be invoked to address his concerns.

First, despite a high mutational frequency of the SARS-CoV, the ultimate clone that emerges is dependent on positive and negative in-vivo selection; only those clones that have a replicative benefit (even a small advantage) will emerge as the dominant isolate. Since our sequencing method is based on direct analysis of PCR products, the full mutational heterogeneity in a viral population from one individual cannot be estimated. For example, a mutation that is present in only one in 1000 viruses within one isolate will simply not be detected, nor is it likely to be biologically important.

Second, only a fraction of the viral particles present in bodily fluid is capable of infection, with that fraction highly dependent on the presence of antibodies, the viral load of the
patient, and the source of the body fluid, and the amount of time that the fluid is out of the host’s body. Thus, Wood’s assumption that every viral particle in a host could be infectious and equally capable of passage is incorrect and would result in a gross overestimate of in-vivo viral genetic diversity.

Third, the dynamic of the SARS epidemic is dependent on infection by a small number of so-called superspreaders. This pattern would, in effect, result in the clonal expansion of a limited number of viral isolates in this SARS-CoV epidemic. Taken together, clinical and in-vivo studies of limited isolates from early branch cases derived from only two or three index cases can be expected to show modest genetic diversity severely restricted by chance events, such as case contacts, and by biological selection.

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Public policies of development in Latin America and Chagas’ disease

Sir—Colonisation with deforestation is one of the most dynamic processes of ecological and social changes in Latin America today. Government policies provide incentives for large-scale agriculture and cattle ranching,1 but growing numbers of producers are investing in cattle production. In Panama, after World War II, the government encouraged rural colonisation, and in 1950–60, many migrants from the hinterlands settled close to the transit zone of the Panama canal.2 This waterway triggered a process of urbanisation and the high rate of infection by T cruzi (60% of the adult population),3 the high rate of A butyracea infestation (up to 100%), and occasional registry of cases of Chagas’ disease, make us think that, in the absence of domiciliation of the insect species, transmission occurs as a result of frequent contact between the wild insect and people inside houses. In La Cascada (Arraiján district), we found up to 20% of children younger than 15 years old had positive seroprevalence for Trypanosoma spp and 36% of pet dogs tested positive for T cruzi. Thus, policies of urban and rural development have not only transformed Panama’s tropical rain forests, but also had long-term health effects and increased costs to the public–health service.

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4 Samudio F, Jabin D, Calzada JE, Romaha CA, Romero Ll, Ortega-Barría E. Molecular characterization of Trypanosoma cruzi isolated from Rhodnius pallescens in Panama. 51st annual meeting of the American Society of Tropical Medicine and Hygiene; Nov 10–14, 2002, Denver, CO, USA.

Adrenal insufficiency

Sir—Congratulations to Wiebke Arlt and Bruno Allolio (May 31, p 1881) for summarising the major issues with respect to diagnosis and management of adrenal insufficiency.

We wish to emphasise the challenges as regards long-term management of Addison’s disease, especially with respect to crisis prevention. In this context, we note that Arlt and Allolio identified a rate of adrenal crisis needing hospital admission almost three times higher in women with primary autoimmune adrenals than in patients with secondary adrenal insufficiency.

In our opinion, all patients with Addison’s disease should be issued with an emergency injection kit of 100 mg hydrocortisone and receive regular training in crisis prevention, including how to administer the injection. However, at present, many members of the UK Addison’s Disease Self-Help Group receive limited or no follow-up instruction in how to deal with illness or injury after their initial diagnosis. Some are issued an injection kit without clear guidance as to when they should use it and with no training for their partner in how to administer the injection.

In instances in which members of the Addison’s Disease Self-Help Group have needed emergency treatment, we are aware that a delay of less than 2 h can see someone close to death through a precipitate drop in blood pressure. If all patients with Addison’s disease were issued with an injection kit, which could be administered at home while waiting for the ambulance, future near-death experiences could be prevented and the risk of permanent disability through respiratory failure or stroke induced by low blood pressure avoided.

Nowadays, individuals with Addison’s disease are typically placed on replacement doses of hydrocortisone, which are frequently less than half the dose that was often administered in the 1970s. More recently diagnosed patients do not, therefore, have the same cushion of excess serum cortisol in their blood to surmount physical challenges, such as strenuous exercise or infection. Some older patients on anachronistically high doses report an ability to shrug off injury and infections, which would undoubtedly bring a patient on a lower replacement dose close to crisis (see http://www.adshg.org.uk for case examples). Moves within the profession to encourage lower daily doses and no training for their partner in how to administer the injection.

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