Downregulation of REST expression is important for enabling the synthesis of genes that permit precursors to attain a differentiated neuronal phenotype. An example of this effect was described by Ballas and colleagues, who showed that forced expression of REST in PC12 phaeochromocytoma cells blocked the normal differentiation of these cells to a neuronal phenotype induced by nerve growth factor. REST has been shown to function in association with a complex of other proteins that permit histone deacetylase enzymes to bind to chromatin. This property may be expected to alter the state of acetylation of key lysine residues on histone molecules, thereby modifying chromatin structure and gene expression. Interestingly, Bahn and colleagues also found that the expression of several other genes that are not known to be controlled by REST was unaltered in Down's syndrome, thereby establishing the specificity of the deficit.

If downregulation of these REST-controlled genes was truly important in the genesis of Down's syndrome then, Bahn and colleagues argue, they should find deficiencies in the normal development of neurospheres into neurons. They therefore compared the effect of culturing wild-type and Down's-syndrome-derived neurospheres under conditions that encouraged differentiation. In this case neurospheres were plated on a laminin substrate in the absence of appropriate mitogens. Under these circumstances, over half of the cells in the Down's syndrome neurospheres did, and they were grossly deformed, with little dendritic development.

These observations are clearly important in the understanding of the cellular and molecular processes that give rise to Down's syndrome. It seems that the expression of a particular group of genes critical for neuronal development is being selectively disrupted, a factor that could certainly account for many features of Down's syndrome. If so, then manipulation of these genes in murine and human models of the disease should favourably alter disease progression. Further investigations should indicate whether members of this group of molecules constitute reasonable targets for drug or gene therapies.

However, the data obtained by Bahn and colleagues is still very preliminary. For example, their conclusions will have to be confirmed by actual measurements of many of the key proteins involved, as opposed to mRNA. Furthermore, there are some odd features about the key proteins involved, as opposed to mRNA.

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Pulmonary oedema at moderately high altitudes

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It has been recognised for centuries that there are health hazards associated with ascent to high altitude, and since the 19th century the physiological effects of altitude have been known to be due not to the reduction in ambient barometric pressure per se, but rather to the decrease in the pressure of inspired oxygen that occurs as barometric pressure falls. The three manifestations of acute altitude sickness are:

- acute mountain sickness (AMS), which is characterised by an altitude-related headache that is accompanied by symptoms such as malaise, fatigue, gastrointestinal symptoms (anorexia, nausea, even vomiting), dizziness, or sleep disturbance;
- high-altitude pulmonary oedema (HAPE), a non-cardiogenic form of pulmonary oedema that typically presents as dyspnoea, cough, and chest compression, with crackles on examination, accompanied by tachypnoea, tachycardia, and even cyanosis, and pulmonary infiltrates in the chest radiograph, often distributed patchily; and
- high-altitude cerebral oedema (HACE), a dreaded condition that results in ataxia, altered mental status and, if progressive, death from cerebral herniation.

The incidence and severity of the various altitude illnesses depend on factors such as the rapidity of ascent, the final altitude achieved, residence at a low altitude, and it is reported in up to 25% of individuals who ascend to altitudes of up to 3000 m, and in more than 40% at altitudes above 4000 m. By contrast, clinically severe HAPE has been reported to occur less frequently, typically in 5% or fewer of adults who ascend to altitudes above 3500 m. Certain individuals do seem to be especially prone to HAPE, and will commonly experience recurrences on re-ascent. Importantly, unlike uncomplicated AMS, HAPE can be life-threatening. HAPE has a reported mortality of 44% if untreated, compared with 6% among those who receive supplementary oxygen, descend to a lower altitude, or both. In view of these statistics, a prudent physician might reasonably surmise that any clinical evidence of pulmonary oedema at altitude (such as crackles on examination) is a strong indication for supplementary oxygen and descent.

The view that pulmonary oedema is an uncommon but severe occurrence during climbs to moderately high altitudes is critically examined in a well-conducted prospective study by George Cremona and colleagues reported in this issue of The Lancet. Using highly sensitive methods to detect evidence of pulmonary oedema (including closing volumes, chest radiography, and physical examination), the investigators found radiographic or auscultatory evidence of pulmonary oedema in 40 (15%) of 262 people climbing up to 4559 m, and these individuals had on average higher scores on the Lake Louise questionnaire (a research tool that quantifies the symptoms and signs of altitude illness) at the summit than did those without clinical evidence of oedema. Closing volumes were also obtained as a proxy for increased interstitial water, and 74% of individuals tested who otherwise had no radiographic or auscultatory findings nevertheless showed evidence of subclinical pulmonary oedema (ie, a rise in closing volume at altitude). In total, only 23% of climbers studied were free of clinical or
subclinical pulmonary oedema at the summit. However, with the exception of one person who was excluded from the study, none of the climbers developed pulmonary oedema of sufficient severity to warrant evacuation. These results are consistent with past reports (panel) that lung crackles on examination at altitude occur commonly, but are usually of little clinical significance.

What are the clinical implications of these findings? Foremost is the realisation that disturbances in pulmonary-water balance are common at altitudes attainable by many recreational climbers, but fall within a broad continuum in which a substantial proportion of climbers (15–27% at 3600–4600 m) will develop lung crackles. However, only a minority of climbers with crackles are likely to be ill enough from HAPE to justify immediate descent. Thus, the decision to descend or not must hinge on factors other than the presence of crackles, such as whether other symptoms and signs are present, how severe they are, whether the patient is deteriorating, and, if so, how quickly. This decision must also take into account the hazards involved in arranging descent (which can be substantial in the often unforgiving environment faced during mountaineering). If descent is indicated but unduly hazardous, individuals with HAPE can be managed temporarily with supplementary oxygen or treatment in a portable hyperbaric chamber. As therapy for HAPE, nifedipine should be reserved for severe oedema at altitude. In view of the increasing popularity of recreational activities at altitudes capable of producing HAPE, better markers for susceptibility to this disorder are needed.

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<table>
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<tr>
<th>Study</th>
<th>Location</th>
<th>Altitude</th>
<th>Number</th>
<th>AMS</th>
<th>Lung crackles</th>
<th>Clinically relevant HAPE*</th>
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<td>278</td>
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<td>262 §</td>
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<td></td>
<td>0.4%</td>
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*Definition varies from study to study
†Unpublished data as cited by the author and by Hultgren and Marticorena
‡Includes both crackles and radiographic evidence of oedema
§Excludes the one identified case of clinically relevant HAPE, for whom data were incomplete.


Disease severity as a predictor of outcome in scleroderma

The pathogenesis of systemic sclerosis, a complex life-threatening systemic disease that targets the skin, lungs, heart, gastrointestinal tract, peripheral circulation, and musculoskeletal system, is incompletely understood, but the disorder is known to be characterised by tissue fibrosis, small-vascular vasculopathy, and an autoimmune response associated with very specific autoantibodies. Its most striking physical finding, skin thickening, has led to scleroderma becoming the most popular name for this disease; yet the largest group of scleroderma patients have only limited skin sclerosis. Scleroderma is classified into subsets defined by the amount of detectable skin thickening on physical examination. Patients with diffuse cutaneous scleroderma disease have widespread skin...