effects mainly through hypothalamic growth-hormone-releasing hormone (GHRH) and somatostatin-releasing-inhibiting factor (SRIF)[7]. Perhaps Grf-1-dependent regulation of growth hormone synthesis and release is modified in our *grf*1 mutant mice by deregulation of the neuronal network in the hypothalamus. The molecular events that link muscarinic receptors and Ras proteins through Grf-1 (ref. 8) might also be involved in controlling the GHRH/SRIF balance in the hypothalamus and in memory consolidation in the amygdala[9].

Like other paternally expressed genes, *grf*1 is involved in growth stimulation, whereas maternally expressed genes are responsible for growth suppression[10]. In contrast to these imprinted genes that are implicated in fetal growth, *grf*1 is the first imprinted gene to be implicated exclusively in postnatal growth control.

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Miocene/Pliocene shift: one step or several?

Cerling *et al.*[1] provide evidence of a worldwide expansion of biomass of plants using the C_4 photosynthetic pathway about 8–6 million years (Myr) ago, recorded in the carbon isotope composition of the dental enamel of fossil herbivores. The authors claim that the expansion of C_4 plants is accompanied by a "worldwide faunal change" and infer that "an important global ecological change was under way at this time". For these statements to be true, the period of transition from C_3 to C_4 plants must prove to be contemporary with the period of faunal turnover, and both events must have taken place in the same geographic areas. At least, this is what the correlation of faunal and vegetation events provided by Cerling *et al.* seems to indicate.

But this model lacks a detailed analysis of extinction/immigration rates in the framework of precise palaeomagnetic and biostratigraphical data. In this context, a comparison of the late Miocene–early Pliocene records of artiodactyl and rodent communities from Spain and Pakistan is of special interest. First, the amount of palaeomagnetic and biostratigraphical data from both areas[2–8] provides a high resolution of the shifts in faunal communities, and second, according to Cerling *et al.*[1], the C_3/C_4 transition took place all over the world except in western Europe.

Our comparison of extinction and immigration rates from sites in Spain and Pakistan (Fig. 1) reveals that first, in Pakistan's Siwalik sediments, not one but two faunal changes occurred, affecting especially artiodactyls. The first one, at about 10–9 Myr ago, largely preceded the C_3/C_4 transition (8–6 Myr ago); the second one occurred at its end (6.5 Myr). However, none of them exactly coincides with the initial expansion of C_4 biomass (8–7 Myr ago), despite a slight increase in rodent extinctions.

Second, both faunal changes in the Siwaliks are contemporary with faunal turnovers in Spain, although in western Europe there is no indication of C_4 diet at any time. In Spain, these faunal changes turn out to have been even more dramatic than in the Siwaliks as the extinction/immigration rate is twice as high. In Spain, woodland or forest indicators (hominoids and tragulids) became extinct about 9 Myr ago, whereas in the Siwaliks hominoids survived their European counterparts by about 1 Myr, and tragulids by as much as 5 Myr.

In the light of these data, we cannot find synchronicity or even a causal link between faunal and vegetation change. Faunal turnovers of different magnitudes took place before and after the appearance of C_4 plants, suggesting that C_3/C_4 transition and faunal turnovers occurred independently.

The "important global ecological change" instead looks like a succession of faunal and vegetation changes, scattered over a long period of at least 5 Myr. We feel that there is insufficient information to permit a clear interpretation of these phenomena. They probably occurred under the influence of a variety of events such as alpine orogenesis with Himalayan and Tibetan uplift, monsoonal dynamics, increasing seasonality, and other factors not yet fully investigated.

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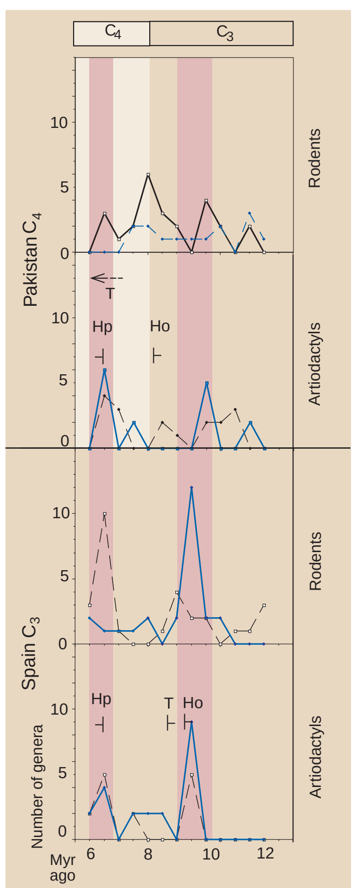

Figure 1 Faunal turnovers in the Eurasian Upper Miocene epoch under C_3 (Spain) and C_4 (Pakistan) conditions. Dotted lines, appearance of genera; continuous lines, disappearance of genera. Hp, hippopotamids; Ho, hominoids; T, tragulids. Data on Pakistan's Siwalik sediments derive from ref. 8; the palaeomagnetic scale is from ref. 9. Considered are herbivore communities with frequent changes at the generic level (artiodactyls and rodents); excluded are groups with low generic diversity such as proboscideans, rhinos and equids. Between 12 and 5.5 Myr ago, two faunal turnovers took place, the older one between 10 and 9 Myr ago and the younger one between 7 and 6 Myr ago. 60% of all faunal changes (immigrations/extinctions) that happened between 12 and 5.5 Myr ago occurred in these times of faunal turnover, when the rate of extinction/immigration increased up to four times the 'normal' value. With the exception of the extinction pattern of Siwalik rodents in the late Miocene epoch, there is a high correlation between the faunal turnover maxima of both the Spanish and the Siwalik herbivore communities, despite the transition from C_3 to C_4 plants at 8 Myr ago in Pakistan.

Cerling et al. *reply* — Köhler *et al.* suggest that phenomena other than floral change may be involved in the late Miocene global vegetation change, such as monsoonal dynamics or unnamed “other factors”. Citing evidence from Spain and Pakistan, they do not believe that there is necessarily a synchronicity or a causal link between faunal and vegetation change in the late Miocene epoch. However, on the contrary, it seems highly unlikely that a vegetation change on the scale documented[1] would be uncorrelated with faunal change.

Widespread faunal change in the late Miocene epoch was recognized[7,10–12] long before the carbon-isotope shift was identified; our work was the first to attempt to link these widespread faunal changes to global vegetation change[1,13]. For example, in North America, Webb *et al.*[14] state that the “boundary between the Early and Late Hemphillian (about 6 Myr ago) records a mass extinction event for equids, when about ten of the existing 18 lineages vanished”. Although it is difficult to ‘prove’ causality in historical events, it seems likely that widespread faunal changes are linked to widespread vegetation changes.

The data from the Siwalik sediments in Pakistan are especially informative, because only from this region are there coeval data on faunal turnover, isotope palaeoecology, and upwelling related to monsoon dynamics (Fig. 1). Smoothed palaeosol data for carbon-13 content ($\delta^{13}C$) show a sharp change starting about 7 Myr ago and continuing to about 5 Myr ago, denoting the shift from C_3- to C_4-dominated vegetation.

The $\delta^{13}C$ data for tooth enamel show that the dietary change, which enhances the C_3 or C_4 signal by selective feeding, can be seen somewhat earlier than in the palaeosols, a result to be expected. Smoothed $\delta^{18}O$ data from palaeosols indicates a change in soil waters that precedes the $\delta^{13}C$ shift and which is correlated with increased abundance of upwelling indicators in the Arabian Sea at about 8.5 Myr ago.

Therefore the isotope record in the Siwaliks records two signals: a change in monsoonal dynamics at about 8.5 Myr ago and a pronounced vegetation change at about 7 Myr ago. Detailed faunal collections from the same region document several important turnover events. The two biggest events are at about 7 and 8.5 Myr ago (Fig. 1) and correspond to the two periods of change recorded in the isotope record.

Although the record is indeed complicated, the stable isotope record documents two important events affecting faunal change in the Siwaliks: one starting about 8.5 Myr ago that is related to the monsoon intensification, and a slightly later event related to expansion in C_4 biomass. Earlier faunal changes, such as those before 10 Myr ago as mentioned by Köhler *et al.*, are unrelated to the global expansion of C_4 biomass.

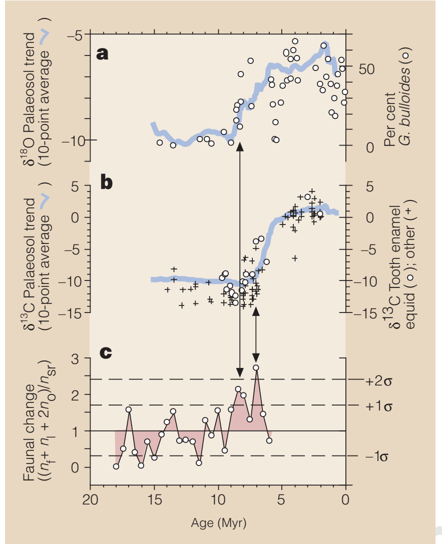

Figure 1 Data from Pakistan's Siwalik sediments show the two biggest events occurring at about 7 and 8.5 Myr ago. **a,** $\delta^{18}O$ data from Silawik palaeosols, representing a trend determined by taking a 10-point running average of the roughly 200 palaeosols from the interval 16 to 0 Myr ago[16]. Also shown is the fraction of *Globigerina bulloides* from the Arabian Sea, an indicator of upwelling related to monsoon dynamics[17]. **b,** $\delta^{13}C$ data for palaeosols and for mammals' tooth enamel[1,18–20] in the Silawiks, representing a trend determined by taking a 10-point running average of the 200 or so palaeosols from the interval 16 to 0 Myr ago[16]. **c,** Faunal change index from the Siwaliks, represented by the number of first (n_f) and last (n_l) occurrences, including only occurrences (n_o), normalized to species richness (n_{sr}). Data from ref. 7. The index is normalized to 1.0 for the total data set.

C_4 photosynthesis is an adaptation to low atmospheric CO_2 levels. Because CO_2 gain and water loss both occur through stomata in C_3 plants, we expect that C_3 plants adapted to aridity would prosper in periods of lower atmospheric CO_2. We would therefore expect that global changes within C_3 flora accompanied the C_4 expansion at the end of the Miocene epoch. Changes within C_3 ecosystems can be related to changes in atmospheric CO_2 levels (for example, the Pleistocene/Holocene transition[15]).

So, although C_4 plants did not flourish in Europe or in other high-latitude regions, it is likely that floral change occurred in those regions within C_3 ecosystems through the Miocene/Pliocene transition. The absence of evidence for C_4 expansion in Europe should not be taken to mean that floral change did not take place in Europe at the end of the Miocene; the isotope record is silent on that issue.

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Life-support system benefits from noise

Mechanical ventilators are used to provide life support for patients with respiratory failure. But over the long term, these machines can damage the lungs, causing them to collapse and the partial pressure of oxygen in the arteries to drop to abnormally low values[1]. In conventional mechanical ventilation, the respiratory rate and volume of air inspired per breath are fixed, although during natural breathing these parameters vary appreciably[2]. A computer-controlled ventilator has now been introduced[3] that can use noise to mimic this variability. We describe a conceptual model of lung injury in which the partial pressure of arterial oxygen is improved significantly by computer-controlled rather than conventional mechanical ventilation, in agreement with recent experimental data[3].

To explain how variability can improve the arterial partial pressure of oxygen (pO_2), consider the pressure–volume (P–V) behaviour of an injured lung that is being mechanically ventilated with many peripheral airways closed, thereby creating large collapsed regions. Let α represent a fraction of the lung that is collapsed at the end of expiration. An uncollapsed lung will be ventilated according to a 'normal' nonlinear P–V relation[4] (see the normalized P–V curve in Fig. 1a, labelled $\alpha = 0$). Collapsed regions, however, significantly alter the P–V curve[5].

The limiting case of $\alpha = 1$ in Fig. 1a shows a model P–V curve for the first inflation of a completely collapsed lung, where V is proportional to P^N (N ranges from 10 to 16)[6]. When α is between 0 and 1, the P–V curve of the entire lung ($\alpha = 0.3$) will be a combination of the 'normal' curve and the P^N curve. Thus, for P values below 0.75, the highly nonlinear P^N term dominates, whereas, for P values above 0.75, the contribution of the 'normal' P–V curve leads to flattening of the P–V relation.

In conventional mechanical ventilation, P increases from end-expiratory pressure $P_{exp} = P_1$ (say $P_1 = 0.3$) to a fixed end-inspiratory pressure $P_{ins} = P_2$ (say $P_2 = 0.7$). The corresponding opened volume in the collapsed region increases from V_1 to V_2. We mimic variability in breathing by adding noise to P_2 so that P increases from P_1 to $P_{ins} = P_2 + \eta$, where η is a random variable changing from breath to breath and is taken from a zero-mean gaussian distribution (Fig. 1b).

Suppose that, for one inflation, P increases to $P_{ins} = 0.75$ rather than to 0.7. This results in gaining recruited volume compared with $P_{ins} = 0.7$. Suppose now that for the next inflation, P increases to only $P_{ins} = 0.65$, losing some recruited volume. Owing to the strong nonlinearity (P^N) of the P–V curve, the 'gain' of volume for $P_{ins} > P_2$ is far greater than the 'loss' of volume for $P_{ins} < P_2$. When P_{ins} samples the gaussian around P_2 many times, the mean of P_{ins} will be P_2, but the mean of the distribution of the recruited volumes will increase from V_2 to V_3. The quantity $\Delta V = V_3 - V_2$ represents the net improvement, which is more than 240%.

Hence surface area for gas exchange in the collapsed region increases, leading to an increase in arterial pO_2. In addition, as lung injury progresses, α increases, and the P–V curve of the entire lung gradually shifts towards the P^N limit. Therefore, with increasing a, adding noise to ventilation should increasingly improve the arterial pO_2, a prediction that is consistent with experiments[3].

The process of varying P around P_2 is analogous to the noise-enhanced amplification of a useful signal in a system by stochastic resonance[7]. In stochastic resonance, increasing the standard deviation (s.d.) of the noise in a nonlinear system will initially amplify a weak input so as to increase the output signal-to-noise ratio; however, further increasing the standard deviation will have the opposite effect. The output signal in our case is the arterial pO_2. When small noise is added to P_2, the surface area for gas exchange, and hence arterial pO_2, increases.

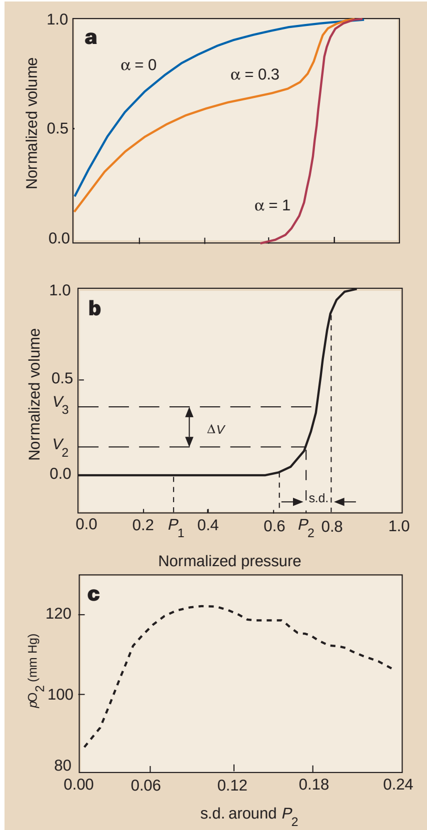

Figure 1 Variability improves arterial partial pressure of lung oxygen. **a,** Pressure–volume (P–V) curves normalized to unity at total lung capacity. $\alpha = 0$, normal P–V of a lung without collapsed regions[4]. $\alpha = 1$, P–V for a collapsed lung[6] where recruitment of volume is proportional to P^{16} for $P < 0.75$. $\alpha = 0.3$, weighted average of the two limiting cases. **b,** Normalized P–V curve of a collapsed region (case $\alpha = 1$ from **a**). P_1, end-expiratory pressure; P_2, end-inspiratory pressure; V_2, corresponding recruited volume. When noise (s.d.=0.075) is added to P_2, average opened volume increases from $V_2 = 0.15$ to $V_3 = 0.363$. **c,** Predicted arterial blood oxygen partial pressure pO_2 as a function of the s.d. of the gaussian around $P_2 = 0.7$. pO_2 data obtained by calculating and averaging 1,000 normalized compliance values, C, which, using ref. 3 data, we relate to pO_2 ($pO_2 = 2.8C + 6$).

Increasing the noise amplitude too much may adversely affect the arterial pO_2. For example, as we gradually increase the standard deviation of the gaussian noise along the S-shaped nonlinearity curve ($\alpha = 0.3$ in Fig. 1a), we find that the normalized compliance, C (defined as $V_T/(P_{ins} - P_1)$, where $P_{ins} = P_2 + \eta$, and V_T is the volume inspired per breath (corresponding to $P_{ins} - P_1$), displays a maximum.

As C is linearly related to arterial pO_2 in lung injury[3] (probably because the collapse of lung regions leads to proportional changes in the area available for gas exchange), our model predicts that there is an optimum standard deviation at which pO_2 also displays a maximum (Fig. 1c). So the possibility of tuning noise for optimal gas exchange in mechanical ventilation arises, from the presence of a nonlinearity due to the competing effects of recruitment of alveoli via avalanches[8] (causing C to increase) and the gradual stiffening of the overinflated parenchymal tissues[4] (causing C to decrease).

As well as offering immediate improvement in gas exchange, noise may have long-term benefits for patients with acute lung injury and respiratory failure because, without requiring increased mean airway pressures, fewer alveolar regions will remain collapsed. This is significant, as high airway pressures cause mechanical failure of pulmonary microvasculature[9], and high shear forces on the alveolar walls increase the level of inflammation which can further propagate the inflammatory response within the alveolar compartment[10]. So including appropriately designed noise in mechanical ventilators will improve gas exchange and could have a significant effect on morbidity by breaking the chain of injury propagation in acute lung injury.

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correction

In "What's so special about figs?" (*Nature* **392**, 668; 1998) the values given in Table 1 for copper, iron, manganese and zinc should have been expressed as μg per g dry matter. Also, in ref. 1, the first author's name should read "Conklin, N. L."