picture of the connections between the nervous system, bone marrow and blood-cell development. Early studies using photomicrographs of neurons in the bone marrow showed that it is innervated by nerve fibres[7]. During the past decade, surgical, pharmacological and genetic denervation models have established the nervous system's role in regulating the HSC niche[8]. But these studies mainly focused on sympathetic nerve fibres (those involved in involuntary actions of the body), showing that they help to maintain the functional integrity of the niche[9]. Here, Gao *et al.* have found that the adhesion of HSCs to their bone-marrow niche and their ability to mobilize to the peripheral blood is controlled by nociceptive neurons acting directly on HSCs through secretion of the neurotransmitter CGRP.

Surprisingly, the authors did not detect neuron-induced changes in the cell-surface levels of CXCR4, CD44 and VLA4 – molecules known to be expressed on HSCs and associated with their trafficking. Future studies, then, will need to delineate the precise mechanisms that mediate HSC mobilization following CALCRL–RAMP1 stimulation. It is also not known whether G-CSF affects nociceptors directly or indirectly through other cell types in the marrow. Such questions can be addressed using cell-type-specific gene targeting in animals. Moreover, findings that might be relevant to humans would need to be validated in clinical trials, because human biology is often not perfectly reflected in mice.

Finally, we should also consider stress responses in the bone marrow and their effects on neurons: for example, leukaemia induces nerve damage in the marrow[10], so it will be valuable to study the effects of blood cancers and ageing specifically on bone-marrow nociceptors. These issues notwithstanding, a robust molecular understanding of the neural regulation of haematopoiesis is now beginning to emerge.

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This article was published online on 23 December 2020.

Climate science

A seasonal solution to a palaeoclimate puzzle

Jennifer Hertzberg

Scientists have long been baffled by the mismatch of climate simulations of the past 12,000 years with temperature reconstructions from geological records. It now emerges that seasonal biases in the records explain the disparity. **See p.548**

Understanding past climate change is crucial for putting modern global warming in context. Reconstructions of climate during the Holocene – the current interglacial epoch, which began 11,700 years ago – based on geological evidence suggest that a peak in global mean annual temperatures between 10,000 and 6,000 years ago was followed by a cooling trend, which then reversed in the post-industrial era[1,2]. However, computational simulations of Holocene climate reveal only a long-term warming trend[3]. On page 548, Bova *et al.*[4] report an analysis that effectively brings Holocene climate reconstructions in line with computational simulations. This result has important implications for our understanding of the drivers of climate change during the Holocene and for the context of post-industrial warming.

To reconstruct past climates, scientists rely on proxies: geological materials that have properties that can be measured and correlated with modern climate parameters. The apparent temperature peak during the early Holocene (known as the Holocene thermal maximum) is a prominent feature in global syntheses of proxy-based climate reconstructions[1,2] (Fig. 1). Its notable absence from computational modelling has been dubbed the Holocene temperature conundrum, and has puzzled climate scientists for years[3]. The disagreement has been attributed to seasonal biases in proxy reconstructions[5] – that is, the proxies reflect the evolution of seasonal temperatures, rather than mean annual ones – and to deficiencies in modelling[6]. Notably, global proxy syntheses are dominated by sea surface temperature (SST) records (see ref. 2, for example), which are known to be seasonally biased[5].

Bova and colleagues' new method identifies seasonal biases in SST records and enables the calculation of mean annual SST from seasonal SST. It takes advantage of the characteristics of the last interglacial period (128,000–115,000 years ago), which was marked by mild global temperatures, smaller ice sheets and higher sea levels than those of

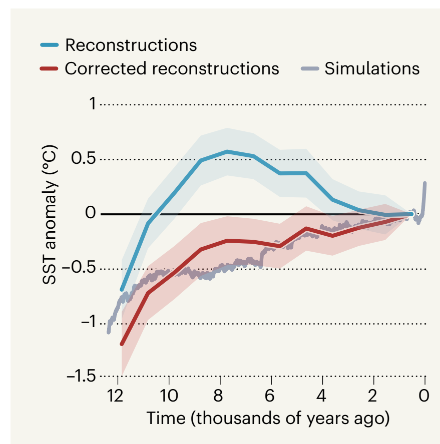

Figure 1 | Correcting seasonal bias in climate reconstructions. Average global temperatures during the Holocene (the current interglacial epoch, which began 11,700 years ago) can be reconstructed from geological records. These reconstructions (blue line) suggest that sea surface temperatures (SSTs) peaked between 10,000 and 6,000 years ago, then declined until the post-industrial period, when temperatures began to rise. However, computational simulations of Holocene SSTs don't match those reconstructions, probably because the geological records are seasonally biased – the records reflect the evolution of seasonal temperatures, rather than mean annual temperatures. Bova *et al.*[4] report a method that quantifies and corrects for seasonal bias in marine geological records, and use it to estimate mean annual SSTs (red line). The corrected data match the computational simulations, thus resolving a long-standing problem in this field. SSTs are shown as anomalies: the difference between the SST of a reference time interval and the average SST between 0 and 1,000 years ago. Shaded areas represent the bounds of one standard error.

today[7]. This period is advantageous for the authors' purposes in that the seasonal difference of incoming solar radiation (insolation) was greater than during the Holocene, whereas the effects of other factors that alter climate, such as greenhouse gases and ice, were weaker, making it easier to identify seasonal biases.

More specifically, the authors' method involves identifying seasonal bias in the portion of an SST record that corresponds to the last interglacial, and in which there was a stronger correlation of SST with seasonal insolation than with mean annual insolation. The sensitivity of the SST record to seasonal insolation during this period is then calculated, and used as a benchmark to remove seasonal bias from the entire record, thereby allowing mean annual SST to be determined from that record. The authors first applied their method to an SST reconstruction based on a proxy taken from a marine site located off the northeast coast of Papua New Guinea. The transformed mean annual SST record was independently validated by applying the new method to SST data for the same geographical region produced in computational simulations of the past 300,000 years – the transformed data matched the mean annual SST output from the simulations.

Bova *et al.* went on to create a synthesis of previously published SST records spanning the last interglacial and the Holocene periods. These records are based on two common proxies used for reconstructing SST: the chemical composition of the fossilized calcium carbonate shells of surface-dwelling unicellular marine organisms known as foraminifera; and organic biomarkers known as alkenones, which are synthesized by marine algae and settle into marine sediments. The authors found that the majority of the examined SST records are indeed seasonally biased.

After converting the seasonally biased SST records into mean annual SST records, Bova and colleagues infer that the climate has been warming since the early Holocene – that is, there is no evidence for a Holocene thermal maximum in mean annual temperatures (Fig. 1). They suggest instead that the Holocene thermal maximum is a seasonal feature driven by a peak in summer insolation in the Northern Hemisphere that occurred during the early Holocene.

The reconstruction of mean annual temperatures produced from the authors' synthesis of proxy records strongly resembles a computational simulation[3] of Holocene climate that also reflects mean annual temperatures – effectively solving the Holocene temperature conundrum. This enabled Bova and colleagues to shed new light on the drivers of Holocene climate change. They find that the increase in global mean annual temperatures that occurred during the early Holocene (12,000–6,500 years ago) was a response to retreating ice sheets, whereas the continued increase in temperatures over the past 6,500 years is due to rising greenhouse-gas concentrations.

The authors also show that mean annual temperatures during the last interglacial period were more stable and higher than their estimates of Holocene temperatures. They attribute this to the near-constant greenhouse-gas concentrations and reduced extent of ice sheets during the last interglacial. Crucially, the researchers find that the current mean annual temperature exceeds those of the past 12,000 years, and probably approaches the warmth of the last interglacial period.

Bova and colleagues' method to identify and correct for seasonal biases in proxy SST reconstructions can now be applied to other temperature records on different timescales. This is a key benefit of their study, because palaeoclimate scientists have long known that temperature reconstructions are probably seasonally biased, but did not have a method for addressing the problem.

One limitation of the findings is that the new synthesis of proxy SST records is limited to the global region between 40° N and 40° S. Proxy records from higher latitudes were deliberately excluded because of the scarcity of such records for the last interglacial, and because of the proximity of those regions to ocean fronts, where ocean dynamics can affect SST. However, the inclusion of these regions might be needed in the future, given that processes at high latitudes have a substantial role in many climate feedback processes. Moreover, the new synthesis examines records based on only two SST proxies. Future work should include more records based on other temperature proxies. Nevertheless, by solving a conundrum that has puzzled climate scientists for years, Bova and colleagues' study is a major step forward for the field.

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Biotechnology

Base editor repairs gene of premature-ageing disease

Wilbert P. Vermeij & Jan H. J. Hoeijmakers

No cure exists for the lethal premature-ageing condition Hutchinson–Gilford progeria. A gene-editing tool – adenine base editors – offers a way to treat the condition in mice. Could this approach lead to an effective therapy? **See p.608**

Gene-editing technologies raise the possibility of tackling the fundamental cause of certain inherited human diseases. On page 608, Koblan *et al.*[1] report their use of such a technology in mice that provide a model for a human accelerated-ageing disorder.

Ageing is influenced by numerous factors – some external, some organ-specific and others systemic, affecting the entire body. It is one of the main biological processes for which the chief cause or causes are not fully known. Often, the mechanisms underlying a biological process are revealed by an analysis of genetic mutants, and mutations in systemic ageing factors are associated with processes of accelerated ageing that affect multiple organs. Most premature-ageing disorders point to problems in DNA maintenance and integrity as the underlying cause. People with Werner or Cockayne syndrome, for example, have defects in different mechanisms that affect genome stability[2].

Generally, premature-ageing conditions exhibit accelerated ageing of a subset of tissues. The best known of such disorders is Hutchinson–Gilford progeria syndrome, which is often referred to just as progeria. Children with this condition look healthy at birth. But, from around one year of age, symptoms begin to emerge, such as growth failure, skin abnormalities and hearing loss. The features of premature ageing increase over time, resulting in striking hallmarks of old age that include wrinkles, loss of fat under the skin, joint stiffness and musculoskeletal abnormalities. However, these children retain a normally functioning