on theories of high-T_c superconductivity. A successful theory needs to explain the physical origin of the kinetic energy lowering and the magnitude, temperature-, and doping-dependence of the observed kinetic energy lowering. It must explain the physical origin of the high-energy scale that gives rise to the observed optical changes in the visible range, and elucidate the mechanism by which the remarkable coupling between this high-energy scale and the low-energy scale of the superconducting energy gap occurs.

Theories that ascribe the pairing mechanism to a magnetic exchange coupling predict an increase of kinetic energy upon pairing (*17*). They thus appear to be inconsistent with the new findings. Theories based on stripes (*18*) and spin-charge separation (*14*) may be consistent with the findings. Kinetic energy lowering has been predicted by these theories, but its expected magnitude must be quantified and the physical origin of the high-energy scale clarified. In the theory of hole superconductivity (*8*), pairing gives rise to lowering of the effective mass of hole carriers, and various predicted consequences (*9*, *19*) appear to be consistent with the reported observations. According to this theory, the same phenomena should also occur in other superconductors (*20*). New theories based on kinetic energy lowering will undoubtedly be formulated.

A new, qualitatively different paradigm for superconductivity is emerging. Carriers pair not because they are happy "being" together, as in the BCS paradigm, but because they are happy "moving" together, even if they are uncomfortable in each other's presence. It is like carpooling with someone one dislikes. The results of Molegraaf *et al.* show that kinetic-energy-driven superconductors, heretofore a theoretical construct, exist. Given that superconductors are defined by the enhanced ability of the carriers to propagate and thereby conduct electricity, this new paradigm makes eminent sense.

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PERSPECTIVES: PALEOCLIMATE

Blowing Hot and Cold

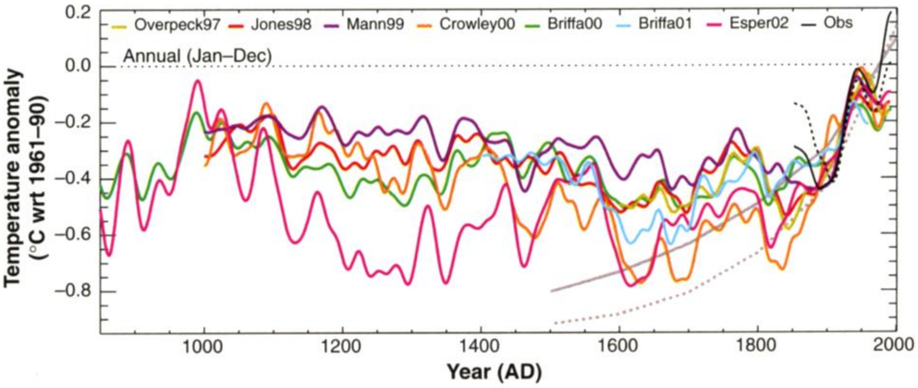
Keith R. Briffa and Timothy J. Osborn

Hiding behind a rather dry title, Esper *et al.*, on page 2250 of this issue, provide a new and important vision of the detailed course of changing temperatures throughout the last millennium (*1*). Their analysis is based exclusively on tree-ring records from 14 locations spread over much of the northern extratropics. Though virtually all previous Northern Hemisphere temperature reconstructions use at least some tree-ring data, the authors use many new data and a processing technique that provides a largely independent history of widespread tree-growth variations, which they scale against modern temperature observations to estimate the relative magnitude of past temperature changes.

The new record differs in several respects from that highlighted in the Synthesis of the Third Assessment Report of the Intergovernmental Panel on Climate Change (IPCC) (*2*), which focused on the 1000-year reconstruction of Mann *et al.* (see the purple line in the figure) (*3*). This record has a smaller amplitude of century-to-century variability and is consistently at, or near, the upper limit of the range of alternate records produced by other researchers (*4*–*8*).

The curve from Esper *et al.* (pink line) shows a pronounced cold phase in the 17th century, in qualitative agreement with the other records and especially with a record of borehole temperature data (see the figure) (*9*), more so when the latter are first gridded to reduce bias due to regional concentrations of these records. The borehole data (and data from Mann *et al.*) are interpreted as indications of true annual temperatures, incorporating both warm season and cold season signals. All records in the figure have been calibrated assuming that they portray annual warmth. It is possible, however, as Esper *et al.* state, that their tree-growth data are more influenced by summer than winter conditions. This affects not only their own record but also a number of the tree-ring series used in other reconstructions shown in the figure.

To place their record on an absolute scale and allow direct comparison of past temper-



Records of past climate. Solid colored lines indicate seven reconstructions of Northern Hemisphere climate: yellow, (*4*); red, (*5*); purple, (*3*); orange, (*6*); green, (*7*); blue, (*8*); and pink (*1*). All records were re-calibrated with linear regression against 1881–1960 mean annual temperature observations averaged over land areas north of 20°N, and the results smoothed with a 50-year filter. The black dotted line shows the estimate that would be made if the predictor was observed warm-season temperatures from the same region, highlighting the difference between warm-season and annual temperature changes during the observed record. Black solid line: smoothed observations, truncated in 1993 when the record of Esper *et al.* ends. Gray lines: annual temperature changes estimated from Northern Hemisphere borehole temperature profiles [dotted line, unweighted average of many sites (*9*); solid line, records gridded before averaging].

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ature changes with 20th century observations, Esper *et al.* scale their series by matching the magnitude of its multidecadal trends to those in Northern Hemisphere mean (land and marine) annual temperatures from 1900 to 1977. After smoothing to remove year-to-year fluctuations, the records can be matched closely with either the annual or summer mean temperatures, because their trends over this period are very similar.

For the early 17th century, annual temperature estimates from Esper *et al.* differ by about 0.7°C from those of Mann *et al.* [see figure 3 of (*1*)]. However, when we regressed the record of Esper *et al.* against nonsmoothed data (see the figure), this difference was reduced to about 0.4°C. Recalibrating both curves against year-by-year warm season temperatures (*10*) reduces this difference further to about 0.35°C.

The results of calibrating any proxy data depend on whether raw or smoothed records are used and on the chosen seasonal temperature predictand. Reconstructions of annual temperature records with predictors that are strongly influenced by summer conditions, assume stationary relationships between proxy and summer climate and between annual and summer climates (and hence between summer and winter). The relationship was stationary over the Esper *et al.* calibration period, but over other periods it may vary: summer warming of extratropical land has progressed at a slower rate than winter warming in the Northern Hemisphere (by about 0.6°C since 1860, see dotted line in the figure) and this is predicted, on the basis of climate model experiments, to continue over the next century at least.

Whatever the true degree of cold in the 17th century, a surprising aspect of the results of Esper *et al.* is the indication of equally cold conditions throughout the 12th, 13th, and 14th centuries, where their reconstructed temperatures are consistently well below those indicated by all other records. On the evidence of this new series, the last millennium was much cooler than previously interpreted. The warming of the 20th century is seen more clearly as a continuation of a trend that began at the start of the 19th century, not the early 20th, and an early period of warmth in the late 10th and early 11th centuries is more pronounced than in previous large-scale reconstructions. This warmth also peaks slightly earlier than could be captured in the shorter Mann *et al.* record and is warmer than in any previous reconstruction.

Even accepting the knotty issue of reconstruction uncertainty, the curve of Esper *et al.* provides evidence for greater climate swings in the last 1000 years than has yet been generally accepted. We need more independent reconstructions like this, based on improved proxy records, and we need to know why it was once so warm and then so cool, before we can say whether 21st-century warming is likely to be nearer to the top or the bottom of the latest IPCC range of 1.4° to 5.8°C (*2*).

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PERSPECTIVES: SIGNAL TRANSDUCTION

Hot *and* Cold TRP Ion Channels

David E. Clapham

Sipping a cold mint julep on a hot summer's day evokes several different pleasurable sensations in the nervous system. Recent papers from McKemy *et al.* (*1*) and Peier *et al.* (*2*) lift some of the mystery surrounding these sensations. These two groups identify an ion channel that is opened (gated) by both cold temperature and menthol, a cooling agent from the mint plant. This ion channel belongs to the transient receptor potential (TRP) superfamily first identified in the photoreceptor cells of the fly. The new channel opens in response to mildly cold temperatures (15° to 25°C), admitting Na$^+$ and Ca^{2+} ions into sensory neurons, which then become depolarized. The sensory neurons that express the new channel are in the mouth, projecting to the brain's trigeminal ganglia, and in the skin, projecting to the dorsal root ganglia of the spinal cord (see the figure). Turn on the hot or cold tap, and out pours hot or cold water. Turn on the TRP channels in nerve cells with heat or cold, and Ca^{2+} ions dribble into the neurons.

The two papers take very different routes to arrive at the same conclusion. McKemy and colleagues have previously identified and extensively characterized the "hot" pepper (capsaicin)/heat (>43°C) sensor, called TRPV1 [VR1 (*3*)], and a related channel TRPV2 [VRL1 (*4*)], which responds to burning heat (>52°C) (*5*). On the basis of published data, and their own experiments on trigeminal ganglia, they hypothesized that an unidentified protein sensed both cold and menthol. Expression cloning has been the key to identifying receptors that mediate other senses such as smell and taste. Although laborious, the method is robust in that it correctly identifies the protein performing a known function. Using this method, McKemy *et al.* discovered that a protein previously identified in prostate cancer cells—and variously called TRPM8, CMR1 (for cold and menthol receptor 1) or Trp-p8 (*6*)—was also present in dorsal root ganglia and trigeminal ganglia of mice, and responded to both cold and menthol.

Realizing that a cold sensor exists in dorsal root ganglia, Peier *et al.* identified a known gene with domains that have homology to the fourth and sixth transmembrane domains of the hot pepper/heat receptor TRPV1. These transmembrane domains were closely associated with gating the channel. Using reverse transcriptase–polymerase chain reaction, they identified the TRPM8 channel in dorsal root ganglia and showed that it was activated by cooling in the 15° to 22°C temperature range, and by menthol. Both studies showed that menthol slightly raises the temperature threshold for TRPM8 activation. McKemy *et al.* also extensively characterized the pharmacological response of trigeminal sensory neurons to menthol and its more potent relative icilin.

The mammalian TRP channel family is defined primarily by structural homology within the transmembrane-spanning domains, but overall sequence identities between members can be quite low. The TRP family were initially classified by Harteneck *et al.* (*7*) into short (TRPC), osm-9–related (TRPV, vanilloid), and long (melanostatin-related, TRPM) channels (*8*, *9*). A 25–amino acid "TRP domain" of unknown function and containing a TRP box (Glu-Trp-Lys-Phe-Ala-Arg) is present in the carboxyl terminus of all TRPC channels, but not in all TRP channels. The amino-terminal cytoplasmic domains of TRPC and TRPV channels contain ankyrin repeats, whereas the TRPC and TRPM carboxyl termini contain proline-rich regions.

Like most of the characterized TRPs that express measurable currents, TRPM8 is relatively nonselective for cations and allows a smaller inward than outward current (*8*). Interestingly, the TRPM8 cold sensor, 1104

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