chronization of cycles, such as the flashing of fireflies.

Stern and McClintock[1] now provide support for the generality of the previous model. They collected body odour on cotton pads from female donors. The pads were wiped above the upper lips (under the noses) of other women (recipients), who were asked not to wash their faces for the next six hours. This procedure was repeated daily over two continuous menstrual cycles. The authors found that the biological clocks of the recipients were affected — the timing of their ovulation and menstruation were systematically changed. Specifically, axillary odours from women in the follicular phase of the ovulatory cycle shortened both the time to ovulation and the length of the menstrual cycle in the recipients. Odours taken on the day that the donors ovulated (and the next two days) delayed ovulation and lengthened the total cycle of the recipients (Fig. 1). These phase-advancing and phase-delaying effects show that human axillary compounds can regulate biological rhythms.

This carefully controlled study clearly shows, for the first time, that the potential for chemical communication involving sexual function has been preserved in humans during evolution. Moreover, humans respond to body-odour signals in a neuroendocrinological manner that is similar to (and, in fact, was predicted from) animal models. However, we still do not have evidence that humans actually do communicate by pheromones in modern society. To test this, we could examine whether a phenomenon such as menstrual synchrony exists in women with no sense of smell. Or we could prevent a social odour from acting in a natural social human situation, and assess the result. Elimination of the phenomenon in such a study would support chemical communication. But a negative result would still not exclude the possibility that pheromones are one of the many modes of human communication.

The finding that humans can communicate by pheromones[1] is, nevertheless, ground-breaking and opens many possibilities for future study and application. The active components of body odours (when clearly identified) could be used as natural, alternative ways to control the time of ovulation; for example, as an aid in contraception. Furthermore, as implied by the authors, we may yet discover that other aspects of our behaviour and physiology are affected by covert olfactory messages from other people during social interactions. Because odours have well-known influences on emotions, perhaps human pheromones complement other sources of interpersonal information. This may result in feelings such as emotional contagion[14] (experiencing another person's feelings), sympathy, empathy and their accompanying physiological reactions. □

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Condensed matter

One substance, two liquids?

Pablo G. Debenedetti

Water, like any other liquid, can be supercooled — cooled below its freezing point without crystallizing. The physical properties of supercooled water are unusual: the lower its temperature, the easier it is to compress, and the more pronounced its anomalous tendency to expand when cooled. Most other liquids contract when cooled, and are more difficult to compress the lower their temperature. As if these characteristics were not peculiar enough, on page 164 of this issue[1], Mishima and Stanley offer new evidence for the notion that two different forms of supercooled water may coexist. Although coexistence of liquid mixtures with different compositions is common, a phase transition between two liquid forms of a pure substance, both lacking long-range order, has never been observed.

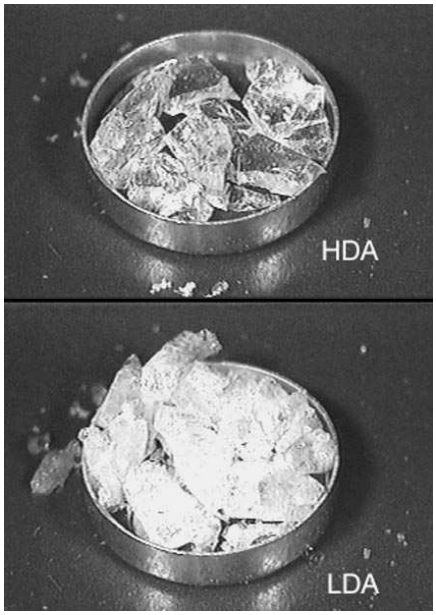

Figure 1 **The two forms of glassy water. LDA is formed by rapidly cooling water at atmospheric pressure; HDA is formed by compressing either LDA or ordinary ice at low temperature. These amorphous solids might be able to coexist, as might two structurally similar liquid waters, LDL and HDL.**

When liquid water is cooled fast enough to avoid crystallization, it forms a glass[2]. Such vitreous water is found as frost on interstellar dust in dense molecular clouds, and comets are made of it[3]. In 1985, Mishima and co-workers[4] proposed the existence of a transition between two forms of glassy water: low-density and high-density amorphous ice (LDA and HDA; Fig. 1). They observed

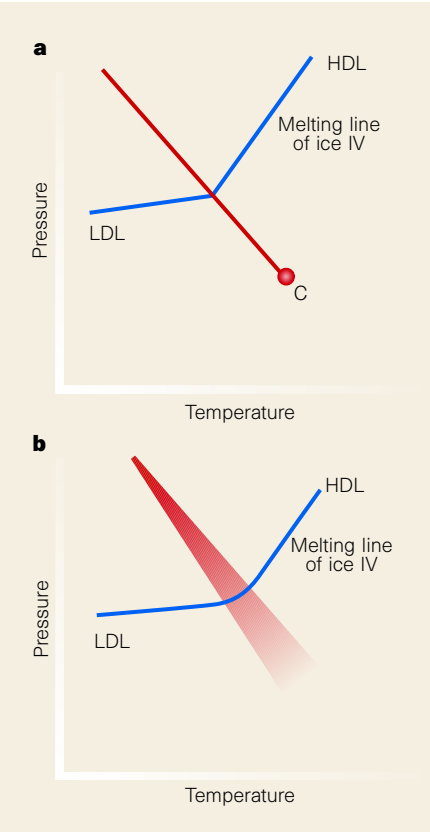

Figure 2 **The melting line of ice IV. The sharp change in its slope implies a sudden change in the density and entropy of liquid water[1]. This could occur,** (a) **along a line of coexistence between a low-density and a high-density liquid (LDL, HDL), terminating at a critical point[5], C; or** (b) **over a limited range of temperatures and pressures that becomes progressively narrower at low temperatures and high pressures[7].**

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sharp changes in volume as a function of pressure, which they interpreted as a phase transition with discontinuities in density and entropy — a first-order transition.

This coexistence between two disordered phases was a bold new idea. In 1992 it was used to explain[5] certain anomalies of supercooled water[6], especially the large increase in properties such as specific heat at low temperature. In this interpretation, the coexistence of LDA and HDA is the low-temperature manifestation of an underlying transition between two liquid phases, LDL and HDL. (In each case, the amorphous ice and the liquid would be separated by a glass transition.) The transition between the two liquids would terminate at a critical point (Fig. 2a), where local fluctuations grow in size, causing the thermodynamic response functions to go to infinity. This second critical point of water would be metastable with respect to crystallization[5].

This hypothesis has remained unproved by experiment, because supercooled water can only be studied above its homogeneous nucleation temperature (–42 °C at one atmosphere), at which spontaneous crystallization occurs. To avoid crystallization, it is necessary to cool water very fast[2] (at about 10^6 °C s^{-1}), and the result is a glass. Mishima and Stanley[1] come very close to overcoming this obstacle. They measure the melting curve of ice IV, a high-pressure form of ice, by decompressing an ice emulsion. The melting curve undergoes a sharp change in slope at the proposed line of liquid–liquid transitions — exactly what should happen if ice IV is melting into two different liquids in different regimes.

Is this proof of the liquid–liquid transition hypothesis? Not quite. The density and entropy of the liquid phase might change abruptly, but not discontinuously (Fig. 2b), over a region whose width decreases with decreasing temperature and increasing pressure[7]. This would also explain the sudden change in the slope of the melting curve of ice IV. A third explanation of supercooled water's anomalies is the stability-limit conjecture[8], which does not appear to fit these results. In this interpretation, there is a line along which thermodynamic quantities such as compressibility and heat capacity go to infinity, and beyond which liquid water cannot exist.

Discriminating between the two explanations shown in Fig. 2 requires proof or disproof of coexistence between two phases. This is a trivial matter for, say, a vapour and a liquid. But at much lower temperatures, where non-crystalline water exists in vitreous form, the extraordinarily long equilibration times characteristic of glasses make direct proof of coexistence between LDA and HDA problematic. Furthermore, the sudden change in slope of the melting curve of ice IV occurs near to the line of homogeneous nucleation, where the liquid formed by decompression of ice IV is expected to freeze rapidly. This may call for additional subtleties of interpretation.

Nevertheless, Mishima and Stanley's work provides strong support for the notion that non-crystalline water can exist in two forms. These forms have very different densities: at 77 K, the compression of LDA into HDA occurs with an abrupt decrease in volume[4] of ~22%. Perhaps another parameter is needed to describe the different phases[9], one that can distinguish differences in local structure.

That the transformation from one form of water to the other is discontinuous — that the two forms can coexist — still remains to be proved. But the models shown in Fig. 2 would have the same microscopic cause: the transient and localized formation of low-density and low-energy structured molecular arrangements stabilized by strong, orientation-dependent interactions such as hydrogen bonding[7,9,10].

A definitive physical picture that explains the behaviour of non-crystalline water at low temperatures is still lacking[11]. This problem is intellectually challenging, because of the novelty of concepts such as liquid–liquid coexistence in a pure substance; and it is also of great practical significance, because of the ubiquity of supercooled and glassy water in stratospheric clouds and interstellar dust, respectively, and the technological potential of methods for storing labile biochemicals in supercooled water emulsions or in water–carbohydrate glasses. Few questions about the liquid state of matter appear more intriguing or important. □

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Cardiac development

Transcription and the broken heart

Garry P. Nolan

Congenital heart defects occur in an astonishing 1% of live births[1,2], and fetal heart malformations are implicated in many pregnancies that end in stillbirth or spontaneous abortion[2]. Why, of all the body's complex organ systems, is the heart so susceptible to malformation during fetal development? Genetic factors are probably central to many congenital heart defects, but complicating factors such as environmental toxins or the diet and age of the parents are likely to affect the severity of these disorders. Despite compelling statistics on their incidence, and in the face of exciting genetic progress[3,4] implicating several genes in the developmental programme of the normal heart, we still do not understand biochemically why heart defects are so prevalent. This is mainly due to a lack of the molecular targets that might indicate preventative therapeutic approaches or outline signalling systems for further investigation.

On pages 182 and 186 of this issue, de la Pompa *et al.*[5] and Ranger *et al.*[6] offer tantalizing hints as to how a single transcriptional regulator might link the genetic and environmental causes of one class of congenital heart disorders — birth defects involving valve and septum formation. Both groups specifically mutated a mouse gene that encodes a member of the NF-AT (nuclear factor of activated T cells) family of transcription factors. This gene (*NF-ATc*) is known to act in the immune system[7]. But, unexpectedly, as a result of the introduced mutations, the pulmonary and aortic valves completely and specifically failed to form. These critical valves control the flow of blood from the ventricles of the heart into the arteries leading to the lungs and the main circulation, respectively (Fig. 1, overleaf).

The ventricular septal structure, which separates the left and right ventricles, was also rendered defective by the mutations. Less severely affected (although clearly defective in the study of de la Pompa *et al.*), were the tricuspid and mitral valves, which regulate the flow of blood from the right and left atria into their respective ventricles. The spectrum of malformations found in human hearts more closely resembles the defects seen in the pulmonary and aortic valves of the mouse *NF-ATc* mutants. Human clinical cases only rarely involve the complete lack of all four valves, consistent with the phenotypes observed in the mice. However, as a result of these combined defects observed in both studies[5,6], the mouse embryos died after 14–15 days' gestation.

One of the defects caused by disruption of the mouse *NF-ATc* gene is strikingly similar to a class of human congenital heart diseases. This class describes defects in