those from the TTD mouse or the Xpa mouse separately, have increased sensitivity to the poison paraquat or ionizing radiation. Both of these agents damage DNA, generating some of the same lesions as ROS, which lends support to the possibility that ROS-induced lesions initiate the age-related decline in TTD mice.

The authors propose that a response to stalled transcription at sites of DNA damage is responsible for early aging in TTD mice. In this scenario, a defective TFIIH results in stalled transcription that decreases gene activity and leads to a mild accumulation of DNA damage. Cells respond by undergoing either apoptosis (programmed cell death) or cellular senescence (irreversible cessation of cell division), both of which may contribute to early organismal senescence in TTD mice. In the absence of Xpa alone (that is, with a fully functional Xpd protein), transcription from a damaged DNA template can still take place, possibly because the amount of spontaneous damage subject to NER is low. In combination with TTD, however, the complete absence of Xpa would exacerbate the suboptimal performance of TFIIH, leaving the DNA lesion exposed for a greater period of time; this would result in a further decline in gene activities and an enhanced response. Thus, early senescence in the TTD mouse may be primarily the result of a cellular response to impaired TFIIH at the site of a spontaneous DNA lesion, rather than the accelerated accumulation of DNA damage or mutations.

Although the true nature of the premature aging phenomenon in the TTD mouse is not yet completely understood, there is support for the scenario sketched above. For example, Ku86 knockout mice, which are completely defective in nonhomologous end joining of double-strand DNA breaks, display various symptoms of accelerated aging (*9*). At least part of this phenotype is dependent on p53 (*10*), a tumor suppressor protein crucial for the cellular response to DNA damage that leads to apoptosis or cellular senescence. Interestingly, mice with increased p53 activity exhibit premature senescence (*11*). This supports the notion that at least a part of organismal aging is due to cell death or cellular senescence in response to imperfect genome maintenance.

What does this tell us about normal aging? Although there is no doubt that a single-gene mutation, such as the TTD defect, merely exaggerates certain components of aging processes, these mutations do indicate various molecular and cellular endpoints of normal aging. The continual induction of DNA damage during normal aging ultimately results in genomic instability as exemplified by persistent DNA lesions, various types of mutations, stalled intermediate repair complexes, and transcription interference (see the figure). In addition, this state of genomic instability activates a variety of cellular response pathways. The frequency and rapidity with which these various molecular and cellular endpoints occur over a normal life-span reflect the proficiency of the organism's multiple genome maintenance pathways. Animal models such as the TTD mouse should help us to unravel the various pathways of genome maintenance and their contributions to organismal longevity, while also shedding light on the great diversity of aging-related phenotypes.

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PERSPECTIVES: PALEOCLIMATE

A Fresh Look at Glacial Floods

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We tend to think of continental-scale ice sheets as rather ponderous affairs, inexorably advancing southward over the landscape and then slowly retreating to the north at the end of each ice age. Over the last 20 years, however, evidence has accumulated that this is a misconception. We now know that the Laurentide Ice Sheet—the largest ice-age glacier—was characterized by thin, marginal ice streams flowing rapidly on low-friction beds and was unstable through much of its history (*1–3*). The ice sheet periodically and abruptly discharged massive amounts of ice into the North Atlantic (*4*), and abrupt coolings and warmings occurred throughout the last ice age (*5*).

Two recent papers (*6, 7*) investigate the roles of glacial meltwater and continental drainage in this glacial and climatic instability. Both papers review numerical modeling studies of ocean circulation. These and another recent paper (*8*) suggest that the thermohaline circulation of the oceans is sensitive to changes in the amount and location of freshwater discharge.

Each time the ice sheet advanced beyond the Canadian Shield, it confined large volumes of water in proglacial lakes at the ice margin. This occurred because the ice sheet flowed over low-relief terrain containing large basins (such as those occupied by the modern Great Lakes), because ice flowed up-slope or against preexisting drainage, and because the glacier depressed Earth's crust under its own weight. As various lobes of the ice sheet slithered forward or back, two major types of drainage event occurred.

First, the overall drainage of much of the continental interior was periodically rerouted to different parts of the ocean—the Gulf of Mexico (via the Mississippi River), the Arctic Ocean (via the Mackenzie River), the North Atlantic (via the St. Lawrence and Hudson Rivers), and the Labrador Sea (via the Hudson Strait) (*9*). Second, large proglacial lakes, such as Lake Agassiz, catastrophically drained in conjunction with some rerouting events.

The amounts of fresh water involved in these drainage changes were enormous (see the figure). Baseline flow (that excluding the sudden drainage of proglacial lakes) of some river systems changed by a factor of 2. Lake-drainage floods ranged from ~0.05 to ~0.30 sverdrups (1 sverdrup = 10^6 m^3 s^{-1}) above baseline flow, averaged over a year. The flood that accompanied the final collapse of the ice sheet may have been as much as 4 to 5 sverdrups.

Building on recent reconstructions of ice-age runoff in North America (*9*), Clark *et al.* (*6*) show that as the Laurentide Ice Sheet retreated, each major change in drainage routing coincided with a change in thermohaline circulation, as indicated by changes in the radiocarbon content of the atmosphere and by ocean-circulation proxies in marine sediment cores. The authors focus on the first type of drainage change—the routing of baseline flow—but suggest that catastrophic lake-drainage events during some of the later reroutings

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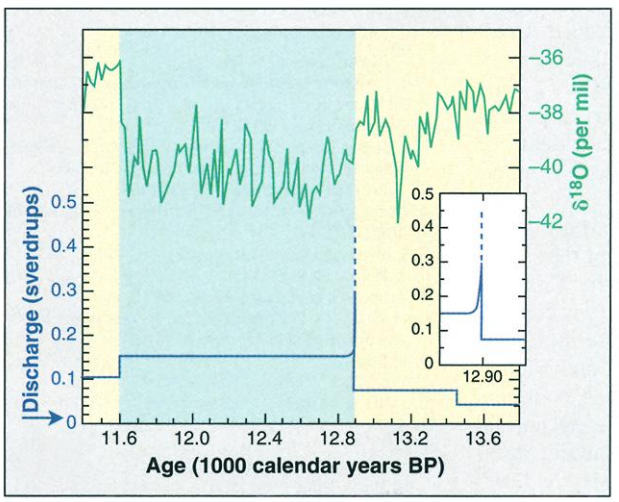
may have sensitized the ocean circulation to changes in the routing of baseline flow. The arguments for coincidence of changes in THC and rerouting events are convincing, but the location and severity of oceanic responses, such as deepwater formation, are poorly known.

Teller *et al.* (*7*) focus on Lake Agassiz drainage events (floods) and their magnitude. They note, however, that the routing of the baseline flow before and after the flood events may have contributed to the effects of the floods on ocean circulation and climate. For example, discharge down the Mississippi before the catastrophic flood through the St. Lawrence at the beginning of the Younger Dryas [12,900 to 11,600 calendar years before the present (cal yr B.P.), calibrated radiocarbon age] may have lowered the salinity in the Atlantic (via the Gulf of Mexico), preconditioning or destabilizing thermohaline circulation before the flood event (*10*). Because the catastrophic flood events coincide with the beginning of rerouting intervals, they are also linked to the climate and circulation changes documented by Clark *et al.* (*6*). Whether their effects persist after the brief duration of the flood events is less clear.



Floods and drainage routing during the Younger Dryas. Reconstructed drainage changes [blue line (*17*)] spanning the Younger Dryas (light blue band), compared with the Greenland Ice Sheet Project GISP2 oxygen isotope record [green line (*18*)]. The Agassiz flood coincided with opening of the 2-million-km^2 Agassiz drainage basin to the St. Lawrence and doubling of baseline flow. It probably lasted a few months to a few years (*7*); the combined outflow is shown (inset, 50 years centered on 12,900 cal yr B.P.) as the average discharge for 1 year (dashed line) and as a yearly average for an exponential decay over 10 years (solid line). Blue arrow: modern discharge of the St. Lawrence River.

For the rerouting events that included flood drainage of Lake Agassiz, the initial flood discharge and the subsequent change in baseline drainage are inseparable, and both were substantial (see the figure). At the beginning of the Younger Dryas, at least three factors potentially affected ocean circulation: (i) preexisting discharge to the Gulf of Mexico, resulting in lower overall salinity in the North Atlantic than today; (ii) an initial large, short-duration flood of fresh water directly to the North Atlantic through the St. Lawrence River; and (iii) a sustained increase, by a factor of nearly 2, in the freshwater discharge down the St. Lawrence. The end of the Younger Dryas also coincides with the end of the eastward drainage routing down the St. Lawrence (see the figure). Modeling studies of the thermohaline circulation have addressed some of these changes, but none has attempted to combine all that is known about the timing and duration of some of the combined rerouting and catastrophic drainage events.

Clark *et al.* (*6*) provide an intriguing explanation for the instability of ice sheets and climate during the last glaciation. When the ice sheet margin was between about 43° and 49° north latitude, small fluctuations in position could lead to major rerouting of freshwater discharge, switching the bulk of the runoff from a vast region on and along the Laurentide Ice Sheet back and forth between the Gulf of Mexico and the North Atlantic. If the effects of rerouting during glacial advance were similar to those during deglaciation (the terrestrial record during glacial advance is poorly preserved), then meltwater discharge could be the ultimate cause of both climatic and glacial instability.

Other explanations for instability have been offered, including a "salt oscillator" mechanism directly linking meltwater and thermohaline circulation (*11*) and a "binge/purge" internal ice-sheet oscillation (*12*). Consistent with these models, the Clark *et al.* model suggests a fundamental instability feedback between oceans and ice sheets. In addition, it provides an explanation for why instability was greatest at times of intermediate ice volume.

The effects of meltwater discharge on lake levels and isotopic compositions of waters in the Laurentian Great Lakes remain unresolved. It has been argued (*13, 14*) that negative isotopic excursions and temporary high lake levels in Lake Michigan were the result of the Agassiz floods, neglecting the concurrent change in baseline flow. Others (*15*) have argued that in Lake Huron and adjacent lakes, the lightest isotopic excursions (greatest meltwater contributions) occurred at times of lowest lake level, not during the rerouting events reconstructed in (*6*, *7*).

This latter interpretation implies that the rerouting events and Agassiz floods had little effect on lake level or isotopic composition of downstream lakes. Changes in discharge through the Great Lakes, calculated from mixing models inverted to produce the isotopic records (*16*), also do not match the timing of climatic and circulation changes associated with the rerouting events. They do, however, match meltwater pulses defined by the global sea-level record.

Better marine records are needed to define the timing and location of thermohaline circulation changes during deglaciation and to further test whether circulation changes indeed coincide with the drainage rerouting events. Numerical models need to use the most recent estimates of drainage location, amount, and sequence to test the plausibility of postulated effects on the thermohaline circulation. Instability of climate and ice sheets during the ice ages may now be generally accepted, but we still have a way to go before we fully understand the processes that produce this instability or the controls and timing of what has occurred.

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