microglia come from? What signalling pathway leads to the release of BDNF from microglia? How does BDNF–TrkB signalling alter E_{anion} in lamina I neurons — could it perhaps lead to reduced synthesis of the KCC2 chloride transporter in the same neurons, or are TrkB receptors activated on other spinal cells that then influence lamina I neurons? Finally, what is the underlying circuitry that mediates the sensation of neuropathic pain when the actions of GABA and glycine are disrupted in the lamina I pain pathway?

Coull and colleagues' results provide an optimistic outlook for the treatment of neuropathic pain, because disrupting BDNF signalling was able to reverse established allodynia in the rat model. This suggests that continuous microglial–neuronal signalling is required to maintain allodynia, and that it may be possible to treat the condition even after the neuropathic pain state is established. ■

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EARTH SCIENCE

Volte-face in the Punjab

Philip A. Allen

Rivers are the great conveyor belts that carry sediment from mountains to the sea. In the Punjab — the Land of Five Rivers — a wholesale shift occurred in the past that re-routed sediment to different oceans.

Rivers don't come much bigger than the Ganges and the Indus, both of which drain the mighty Himalaya. However, as Clift and Blusztajn[1] show in this issue (page 1001), size does not mean permanence. Around five million years ago, the rivers of the Punjab evidently shifted from flowing into the Ganges system and the Bay of Bengal to flowing via the Indus system into the Arabian Sea. This major diversion of continental drainage has been deciphered from the isotopic signature of minerals collected from the Indus fan, a vast undersea cone of sediment stretching for more than 1,000 kilometres from the mouth of the Indus River.

It is well known that rivers shift their courses — switching of the position of the main channel within a river valley is historically well documented, and typically takes place at intervals of decades to thousands of years. Many of the lowland tracts of the world's major rivers, which flow through some of the most densely populated parts of the Earth's surface, and which were the sites of long-since-disappeared civilizations, contain a remarkable record of such switches. The Po of northern Italy and the Huang He (Yellow River) of eastern China are excellent examples. But what is less well understood is the wholesale shifting of river courses at the longer timescales described by Clift and Blusztajn.

The total amount of sediment discharged into the world's ocean is about 20 billion tonnes per year[2–4], and a high proportion of this global annual budget comes from the river systems of southeast Asia, from the Indus to the Huang He[5]. The sediment dumped onto the sea bed of the Indian and western Pacific oceans over the past tens of millions of years has created a vast apron, a few kilometres thick near the mouths of the major rivers, which gradually thins seawards over distances of several thousand kilometres. Scientists are increasingly piecing together the record of past climatic and tectonic events sealed in these deep-sea sediments. On the one hand, measurements of the volumes of these deposits allow variations in the erosion rates of the Asian mountain belts over time to be estimated. On the other, distinctive chemical fingerprints in the sediment permit an evaluation of where the sediment came from in the first place. A combination of the two methods yields a picture of a highly dynamic hinterland in terms of tectonics, evolving topography and river discharge.

Clift and Blusztajn[1] reconstruct the discharge of particulate sediment of the ancient Indus River over the past 30 million years using data obtained from seismic surveys of the sediment on the floor of the Arabian Sea. During this time, the collision of India with Eurasia has formed the mountains of the Himalaya, a bountiful source of sediment for the rivers draining into the ocean. The chemical fingerprint of the sediments of the Indus fan is the rare-earth element neodymium[6]. This is expressed as ϵ_{Nd}, which is related to the ratio $^{143}\text{Nd}/^{144}\text{Nd}$ compared with a standard for the Earth, and is sensitive to the type of source rocks.

The currently low values of ϵ_{Nd} in modern Indus River sands appear to be part of a trend that started after five million years ago. Strongly negative ϵ_{Nd} values, typical of the sediments of the Bengal fan, are thought to be supplied by sources in the Himalayan mountain ranges marking the frontal zone of crumpling between India and Asia. More positive ϵ_{Nd} values are associated with source areas located behind the Himalaya, particularly in the Karakoram Range of northeast Pakistan, which is drained by the headwaters of the Indus. So Clift and Blusztajn make the intriguing connection that

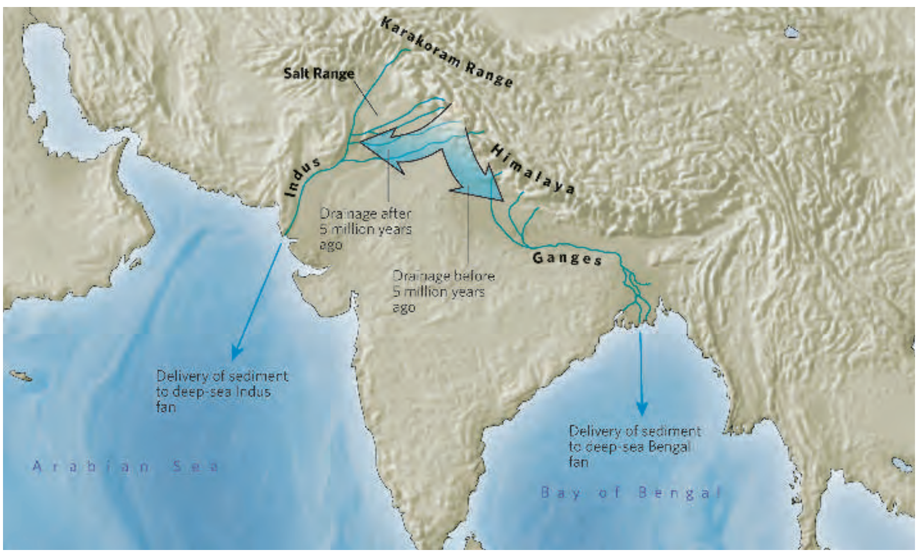


Figure 1 | Drainage of the Himalaya. The map shows the configuration of rivers as it is today, with the rivers of the Punjab flowing into the Indus and delivering sediment into the Indus fan in the Arabian Sea. According to Clift and Blusztajn's[1] analysis of neodymium isotopes in sediments, however, before about five million years ago the Punjabi rivers instead flowed southeast (see Fig. 1b of the paper[1] on page 1002), delivering sediment into the Ganges and the Bengal fan. The growth of the Salt Range is one possible contributory factor to this diversion. Others are flexing of the Indian tectonic plate in response to mountain building and erosion, and the effects of climate change on river discharge.

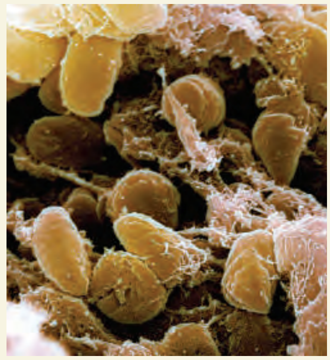
MICROBIOLOGY

Perspectives on plague

The bacterium *Yersinia pestis* (pictured) is notorious as the cause of bubonic plague. When it is breathed in, however, it also causes the rarer but deadlier pneumonic plague. The pathology of this disease in humans and animals is fairly well understood, but much less is known about the earliest stages. Wyndham W. Lathem and colleagues (*Proc. Natl Acad. Sci. USA* **102,** 17786–17791; 2005) have developed a mouse model of pneumonic plague that gives perspectives on these stages as experienced by the host and by the bacterium.

The team infected mice with *Y. pestis* through the nose, and the animals developed a disease that closely resembled pneumonic plague in humans. Bacterial numbers in the animals' lungs increased massively in the first 24 hours after infection. Yet when the authors studied the levels of inflammatory molecules normally produced during an immune response, there was little change during this period. So the bacteria must have a potent anti-inflammatory activity that allows them to become established before the host immune system detects them. After 48 hours, the levels of inflammatory molecules escalated, showing that the mouse immune response does eventually kick in; but it would seem to be too little, too late.

And what happens in *Y. pestis*? A microarray analysis showed that there is a change in the expression of about 10% of the bacterium's genes after it infects its host. Notably, many of these genes are associated with virulence, and in particular with the so-called type III secretion system. This system was already known as a potential means for the bacterium to subvert its host's immune system by altering the types and amounts of inflammatory molecules. That the expression of genes for the system


NIAID/CDC/SPL

is increased in the mice confirms this animal model as biologically valid. Moreover, a comparison with *in vitro* studies showed that the regulation of this system is more complex *in vivo* — suggesting that the model will provide greater insight into this devastating infection. **Helen Dell**

before five million years ago the rivers of the Punjab flowed eastwards as part of the Ganges system to feed the Bengal fan (Fig. 1).

This explanation of the former drainage of the Land of Five Rivers makes sense in the light of the sediments deposited at the foot of the Himalaya, known as the Siwalik Group sediments. These were deposited by ancient river systems that cut into the rising Himalayan mountains, and indeed it was previously suggested[7,8] that there was a continental-scale flip-flop of drainage between the Bengal and Indus sinks. The real value of these new results[1] is therefore not the idea that drainage diversion can occur on a continental scale, but that the isotopic data from the deep-sea Indus fan provide such striking support for that view.

We are now developing a more dynamic impression of the way in which sediment is routed from mountains to the sea. Such routing is strongly influenced at a relatively local scale by the emergence of new mountain ranges in response to continuing continental convergence. For example, the growth of the Salt Range of northern Pakistan may have triggered the diversion of the main tributaries of the ancient Indus to the Arabian Sea. But at the larger scale there are the subtle changes in regional floodplain slopes caused by the flexing of the Indian tectonic plate in response to the growth and erosion of the adjacent mountain belt, whose great mass acts downwards — like a swimmer on the end of a diving board. The longitudinal sediment-filled troughs produced by such flexural downbending[9], known as foreland basins, are particularly prone to major diversion of river systems flowing along the axis of the basin. Unlike steep rivers in tectonically uplifting mountain areas, which cut down into bedrock like cheese wires, low-gradient rivers in foreland basins are easily deflected. Continental-scale diversion might also result from the effects of climate change on river discharge, which may allow one river to dominate its neighbours and capture their drainage systems.

Clearly, investigators attempting to interpret the sedimentary record of the deep sea must be careful to disentangle the effects of climate change, variations in tectonically driven erosion, and continental-scale switches of river drainage. The use of a range of isotopic signatures in river and deep-sea sediments will help in this challenging undertaking. ■

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DEVELOPMENTAL BIOLOGY

A message to the back side

Wolfgang Driever

Vertebrate embryos from fish to mammals seem to use different routes to work out which way is up and which side is front. Yet a novel system involved in defining the dorsal side of fish might be conserved in mammals.

Vertebrates have many developmental processes in common; but so far, no unifying mechanism that specifies the dorsal–ventral (back-to-belly) axis in the vertebrate early embryo has been found. Egg cells, or oocytes, are in general roughly spherical and have only one axis: animal–vegetal, often characterized by the cell nucleus being in the 'animal' portion and away from the 'vegetal' yolk-rich pole. In amphibians and fish, after fertilization certain protein signals are physically transported from the vegetal region to the future dorsal side, contributing to the specification of dorsal. By contrast, the mechanisms of axis formation in mammals are not understood.

On page 1030 of this issue, Gore and colleagues[1] present evidence from zebrafish that *nodal* messenger RNAs, which encode the dorsal signal protein Nodal, are progressively localized to the cells that go on to form the dorsal side. Surprisingly, this dorsal localization also occurs if sequence elements from human *nodal* mRNA are used instead of the zebrafish ones, indicating an evolutionarily conserved mechanism.

The zebrafish version of Nodal is formally called Ndr1 (for Nodal-related 1) and, like the Nodal proteins found in all other vertebrates investigated, it is involved in specifying dorsal structures and two of the major embryonic