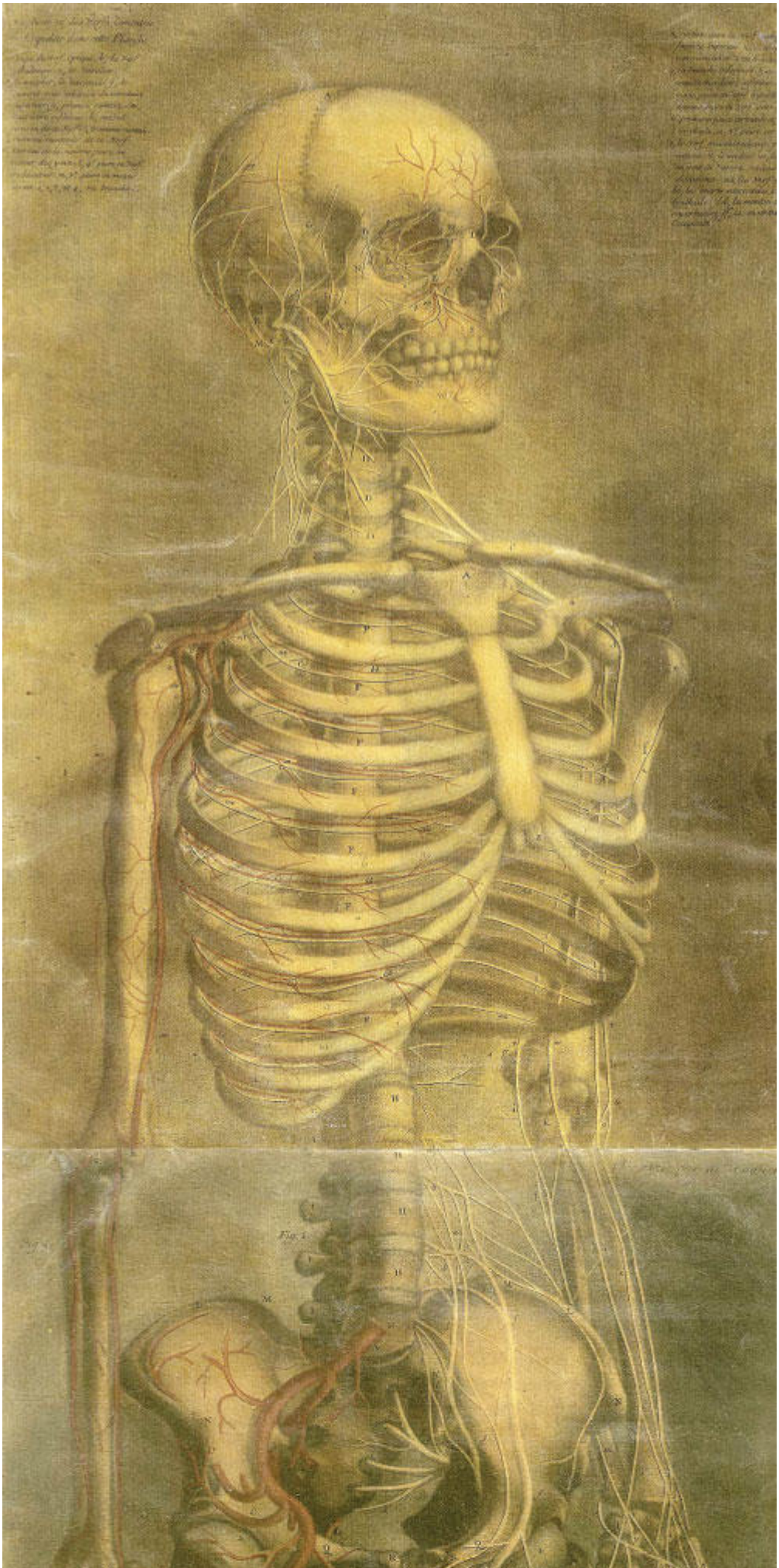
Health & Medicine

Skeleton Key

Fall 2007



When the anatomy illustrator Jacques Fabian Gautier d'Agoty created this four-color mezzotint in the mid-18th century, the skeleton was known only as a physical foundation for the flesh (National Library of Medicine).

We knew our bones were busy producing blood cells and platelets, storing and releasing calcium into the bloodstream, and protecting our squishy innards. Now Columbia scientists have discovered an entirely new function of the skeleton: They say it also acts as an endocrine organ, producing a hormone that helps us process sugar.

Hormones, which control everything from growth to metabolism to reproduction, typically come from our glands or sex organs; a few have been traced to the heart, abdominal organs, and skin. They weren't known to come from bone, until now. A research team led by Gerard Karsenty, chair of the Department of Genetics and Development at Columbia's College of Physicians and Surgeons, has found that osteocalcin, a hormone released by bone cells, directly regulates the metabolism of glucose in mice. Shortages of osteocalcin, the researchers say, seem to cause obesity and type 2 diabetes in the animals.

There is "no guarantee" that the hormone behaves similarly in humans, "but osteocalcin exists in humans," Karsenty says. "It operates in a region where type 2 diabetes genes are known to be present, and its levels vary with sugar metabolism, so we are cautiously optimistic."

In mice, at least, osteocalcin controls blood sugar by increasing the proliferation of insulin-producing beta cells in the pancreas, signaling those beta cells to produce more insulin and triggering fat cells to release another hormone, called adiponectin, that enhances insulin sensitivity. Mice and men both rely on insulin to sweep sugar from the blood and into cells, where it is used as energy or stored as fat.

If osteocalcin has comparable effects on people, Karsenty says, its discovery could lead to a cure for the 20 million Americans with diabetes, in whom insufficient insulin levels can chronically elevate blood glucose, heightening the risk of heart disease, kidney failure, and blindness.

But the discovery that the skeleton interacts with other organs is stunning in itself, prompting scientists to reconsider the skeleton's purpose. "It certainly has caused quite a stir," Graham Williams, an endocrinology expert at Imperial College London, told the Web site Nature News recently. "People think it's a novel idea, and likely to

turn out to be a paradigm shift."

Karsenty and his team had been searching for a skeletal hormone that communicates with fat since demonstrating in 2002 that leptin, a hormone produced by fat cells, is crucial to regulating bone mass. Given that most bodily systems work as feedback loops, if fat signals bone, it stood to reason that bone might also signal fat. Osteocalcin, already known to be lower in diabetics thanks to earlier studies investigating the link between diabetes and an increased incidence of bone fractures, was thrown into the mix of suspects.

The researchers found that mice genetically programmed to have high levels of osteocalcin don't gain weight or become diabetic even when fed a high-fat diet, while mice manipulated to lack osteocalcin become fat, secrete less insulin and adiponectin, produce fewer beta cells, and develop type 2 diabetes.

Karsenty says his lab will continue to investigate the role of osteocalcin in glucose metabolism, in animals as well as humans, with an eye toward developing novel therapies for preventing obesity, type 2 diabetes, and related disorders.

The study was published in the August issue of the journal *Cell*.

Guide to school abbreviations

All categories >