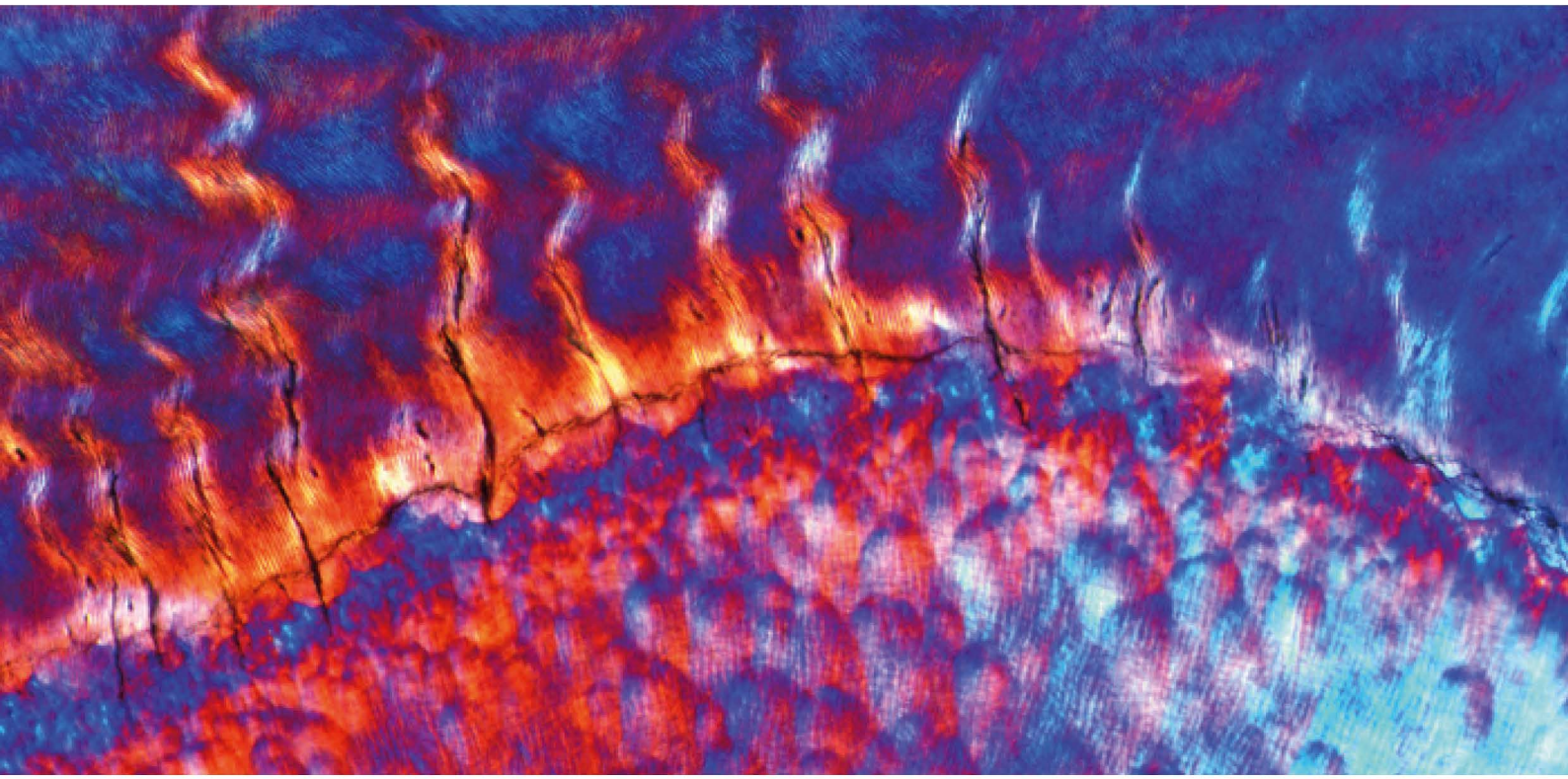

Timothy G. Bromage

Exploring a new lifecycle

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Exploring a new lifecycle

Evolutionary biologist **Professor Timothy G Bromage** has discovered a previously unknown long metabolic cycle, which he uses to study bone and dental samples from humans of sub-Saharan African origin

PROFESSOR TIMOTHY G BROMAGE

To begin, could you give a brief overview of your research and your principal objectives?

Astonishingly, the factors regulating the traits that define the overall life history matrix of any mammal, comprising attributes such as brain and body weight, age at sexual maturity, and lifespan, remains a complete mystery. We are thus particularly curious to know what life history attributes may be inferred from hard tissues and whether this information can be used to reveal the physiological mechanisms responsible for generating life history.

This goal is highly relevant to our overarching aim to understand how life history evolution takes place and how much of the life history arc is interpretable from bone and tooth microscopic anatomy.

You are assessing the extent to which long period biological rhythms may contribute to a general theory of metabolism-mediated life history. What are the implications of this research for human health?

An understanding of long period biological timing will have profound consequences for human health. Metabolism is responsible for energy allocations that fuel all aspects of life history, exerting primary control over the pace and pattern of life. Moreover, as all life history traits reflect dependence on rate and time, it follows that metabolic rate must be inextricably linked to a biological timing mechanism. At small time scales, the daily biological, or circadian clock regulates metabolism and apportions energy for the building, functioning, and maintaining our bodies. However, while the circadian clock may appear key, it has been impossible to link these daily oscillations that all mammals share to the enormous life history variation that mammals express. We thus suggest that long period regulation of metabolism operates to maintain our life history, and that disregulation of how metabolism and life history interact leads to metabolic, developmental, and reproductive disorders and reductions in lifespan.

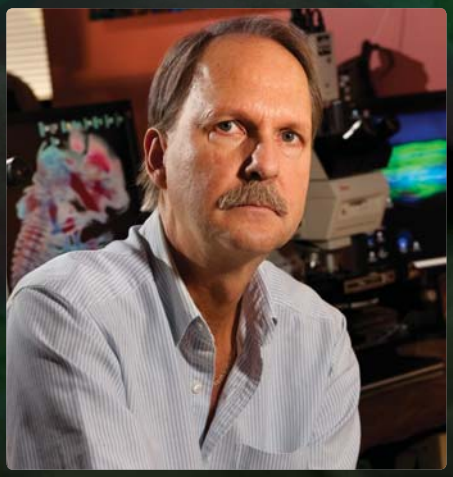
In particular, how could your research impact on the treatment of cancer patients and candidates for stroke and heart attack?

A near-weekly periodicity in heart rate and blood pressure has been demonstrated in humans, which relates to the long period rhythm of an average of nine days in females and eight days in males. Stroke and heart attack tends to occur during specific stages of the daily biological rhythm, but there is likely a near-weekly risk to which people are presently completely unaware.

To have long period information about someone at risk will help clinicians to carefully time preventative medications and to diminish morbidity and mortality. For medications on longer-term regimens, such as for chemotherapy, there will be an advantage to knowing what day of the week is best for a patient to receive treatment. This is particularly so because one of our subsidiary hypotheses concerning long period metabolic rhythms is that it operates in part by regulating rates of cell proliferation, a hallmark of cancer.

How does this research contribute to initiatives concerned with mineralised tissue biology, anthropology, and bone ageing?

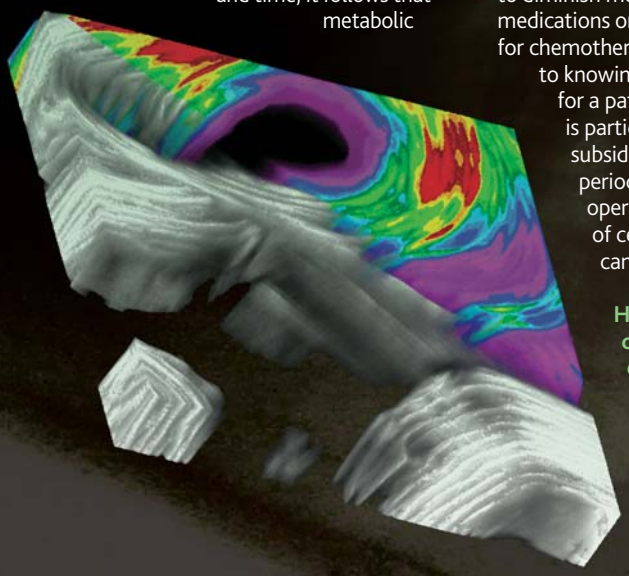
We have learned how to link bone microanatomical structures to specific individual life history by developing a technique to assign packets of incremental bone tissue to real calendrical years in which that bone was formed, just as one would do with tree rings.



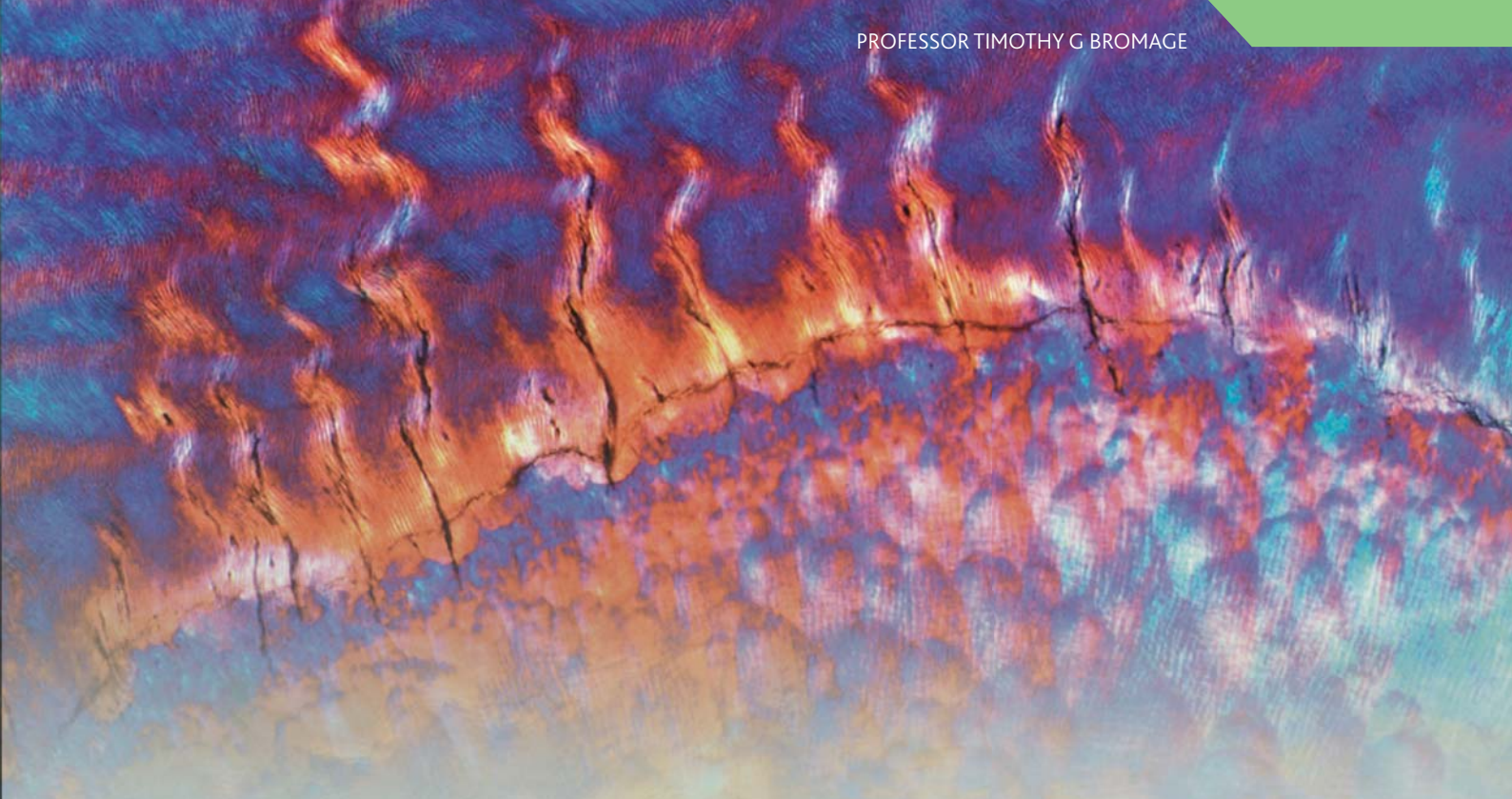
Bone formed in individuals of Bantu origin living through the major 1980-82 Malawi drought is clearly distinguished in its development from bone formed by others before or after that time. Such environmental disturbances have a lasting effect on a person's development.

You are testing your ideas using human bone and tooth specimens and life history information gleaned from questionnaires given to donor next of kin. What are the major challenges associated with this research?

The major challenge associated with our research is that which is common to all science, which is that we don't know what we don't know. We have concluded that a solution to this vexing challenge will not come by means of a search for specific answers because, in all honesty a straight path from what we know now to any one particular answer does not exist. Instead, we must ask the questions that most intrigue us, and let the research take us in its multifarious directions, despite the conflict this may generate with how we must prepare our grant proposals and write our scientific papers.



3D IMAGE OF BLOOD CANAL (TOP) AND INCREMENTAL BONE LAYERS



The secrets **buried in our bones**

A trail-blazing study at the **New York University College of Dentistry** has unearthed a previously unknown metabolic cycle in humans and other mammals that is casting light on the life histories of the dead

EVEN LONG AFTER humans and mammals die scientists can discover many facts about individual life histories just by studying their skeletons. By evaluating microscopic features in bones and teeth it is possible to know details such as body size and life span. But the extent to which human attributes and lifestyles can be interpreted from studying hard tissues is still not fully understood and this has led a team of researchers at the New York University College of Dentistry to dig deeper.

They aim to reconstruct the life histories of humans and mammals in general and to find out to what extent it is possible to understand the physiological mechanisms responsible for generating life history. It is hoped that a greater understanding of how a life history is attained will shed light on important questions such as how the lives of humans are patterned compared to the lives of other species. Ultimately, this research could lead to a general theory of metabolism-mediated life history and such new knowledge may have significant applications to human health.

INVESTIGATING BONE AND TOOTH SAMPLES

To carry out this research the group, led by Professor of hard-tissue biology Timothy Bromage, teamed up with the University of Malawi College of Medicine (UMCOM) to investigate bone and tooth samples of sub-Saharan Africans of Bantu origin. They took 11 whole or 10 cm-long mid-shaft segments from the right and left sides of Bantu cadaveric skeletons, from head to toe, which includes one-half of the lower jaw and its teeth. The data obtained from these samples was then compared to the skeletal material collected from people of Australian Anglo-Celtic heritage, from the Melbourne Femur Collection (MFC).

The team examined dental enamel for incremental lines which represent a daily formation rhythm and another long period rhythm that occurs at some multiple daily events, known as the striae of Retzius. It was Bromage's findings from primate dental enamel that evidence for a long period metabolic clock first came to light. He termed this period the 'Havers-Halberg Oscillation' (HHO), in reference to Clopton Havers who was the first to observe and describe the lamella in bone and the striae of Retzius in enamel, and Franz Halberg, the long-time explorer of long-period rhythms.

UNDERSTANDING GROWTH

The number of days between adjacent striae of Retzius is known as the repeat interval (RI); the interval is a manifestation of the rhythm, it is incidental to this rhythm, not the rhythm itself. The RI is related to body mass and is also the period at which the lamella forms in bone. In non-human primates the RI ranges between two days in the smallest primates and 11 days in the largest. However, when examining the Bantu sample the team found the converse to be true, that larger people have short RI and smaller people have long RI. In humans the RI varies between six and 12 days, with a mean female RI of 9.2 days, somewhat longer than the male mean of 8.6 days. This was an exciting finding, as Bromage explains: "This agrees with our discovery that the repeat interval in enamel is that same period required for the bone forming cells to make one increment of bone, the lamella. Bone mass scales to support body mass, so the bones of larger people become large by creating each lamella in, say, only five days, while smaller people may make the same sized lamella in 10 days".

REVEALING LIFE HISTORIES

To probe further into how long period rhythms regulate body size and life history, relatives of the Bantu sample were asked to complete a questionnaire about the socioeconomic and medical history of the donor. By comparing this information to measurements of the bone and tooth

INTELLIGENCE

HARD TISSUE RESEARCH ON SUB-SAHARAN AFRICANS OF KNOWN LIFE HISTORY

OBJECTIVES

To test novel hypotheses regarding relationships between both bone and tooth microanatomical characteristics and human body size and life history, and to compare peoples of different regional human population origins.

KEY COLLABORATORS

Dr John Chisi, University of Malawi College of Medicine, Blantyre, Malawi • **Dr John Clement**, Melbourne Dental School, Melbourne, Australia • **Dr Haviva Goldman**, Drexel University College of Medicine, Philadelphia, Pennsylvania, USA • **Dr Russell Hogg**, Florida Gulf Coast University, Fort Myers, Florida, USA • **Chen Hou**, Missouri University of Science and Technology, Rolla, Missouri, USA • **Dr Bin Hu**, New York University College of Dentistry, New York, New York, USA • **Dr Yusuf Juwayeyi**, Long Island University, New York, New York, USA • **Dr Rodrigo Lacruz**, School of Dentistry, University of Southern California, Los Angeles, California, USA • **Drs Friedemann Schrenk** and **Ottmar Kullmer**, Research Institute Senckenberg, Frankfurt am Main, Germany • **Dr Igor Smolyar**, National Oceanic and Atmospheric Administration, Silver Spring, Maryland, USA

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TIMOTHY G BROMAGE obtained both his PhD and MA in Biological Anthropology from the University of Toronto. He currently directs the Hard Tissue Research Unit (HTRU), a mineralised tissue preparation and imaging technology development laboratory of the Department of Biomaterials and Biomimetics, New York University College of Dentistry.

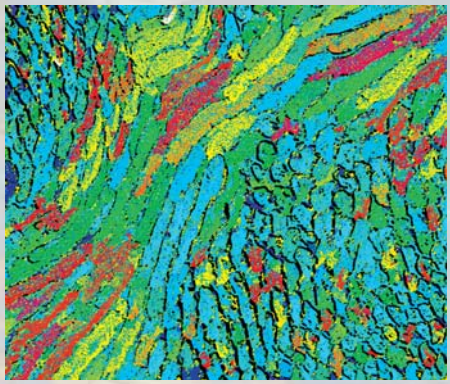
samples, an understanding of how prosperity, diet, body development and external factors affected individuals across their lifespans could be gained: "It was a challenge to integrate reductionist, mostly biomedical skeletal research with the environmental, social, behavioural, economical, and medical factors questions asked of the next of kin," Bromage reflects. "This represented our holistic strategy for understanding human biology; we know that a rural fisherman is more likely to exhibit seasonal growth rhythms than an urban bank clerk."

This combined approach has led to some interesting results, for example, the bone growth of subsistence farmers who lived through the 1980-82 Malawi famine was found to be significantly reduced compared to the urban business population during the same time: "Additionally, our investigations of long period rhythms in the UMCOM cohort are starting to reveal a number of oscillations, some of which are caused by environmental stress, such as drought, but others that may be buried deep into the biology of what it means to be human," reveals Bromage.

Results from the Bantu sample were compared to those of people from Australian Anglo-Celtic heritage and researchers found some important differences. In the UMCOM sample they found individuals had higher bone mass compared to those of the same sex and age from the Anglo-Celtic origin. But the results showed something even more enlightening, as Bromage explains: "The UMCOM bone contains a very much higher proportion of primary bone, meaning bone that has never been remodelled since it was formed. This difference means that the rate of bone being removed from the skeleton during age-related remodelling is significantly less, and thus far less too is the risk of osteoporosis".

LARGEST BONE AND TOOTH BANK

It is apparent that the Bantu sample has a wealth of data to offer scientists and for this reason access to this hard tissue bank has been made open. In fact, the sample now represents the largest public human bone and tooth data bank of people of sub-Saharan African origin and known life history. "Ideas are the clear and ever-present reminder of our times, but the materials of our research, in this case the UMCOM hard tissue samples, endure," Bromage enthuses. "Access is open without any requirement that this material be first published." It is likely that because of the uniqueness of the UMCOM sample there will be opportunities to combine this research with knowledge obtained from other skeletal samples. More information about the UMCOM sample can be found at: www.paleobiomics.org.



HUMAN ENAMEL PRISMS

INVESTIGATIONS CONTINUE

This research offers new insights into how life histories can be reconstructed from the investigation of incremental lamellar bone. For the first time a study of lamellar bone has revealed long period growth rate variability which has never before been observed in humans. What is particularly exciting is the potential they offer for recognising physiological and environmental rhythms and ultimately, the kind of circumstances and lifestyle that an individual experienced when they were alive.

Fascinating results have been unearthed to date, but there are still unanswered questions to be tackled. Further research opportunities in this area include reaching an understanding as to why mammal species have fairly consistent repeat intervals between individuals, yet humans exhibit hugely varying long period cycles between individuals.

By comparing this information to measurements of the bone and tooth samples, an understanding of how prosperity, diet, body development and external factors affected individuals across their lifespans could be gained

human paleobiomics
hard tissue research program

NYU College of Dentistry

SENCKENBERG research