

- 9880 The metabolic disease network
 9931 How rice accumulates arsenic
 10067 Genetic variation reveals misclassifications
 10125 Infected sand flies can transmit thousands of parasites
 10227 Sleep-activated neurons found in the cerebral cortex

APPLIED PHYSICAL SCIENCES

The metabolic disease network

Metabolic diseases tend not to share genes as they interact through the intricate mesh of biochemical reactions that fuel cellular activity. Previous research has suggested that this is because a defective enzyme chiefly responsible for one disease can cause a metabolic intermediate to accumulate or degrade, thus affecting other pathways that have the compound in common. Deok-Sun Lee *et al.* created a metabolic disease network to investigate how shared metabolic pathways contribute to comorbidity (in which a patient suffers from more than one disease at a time). The authors looked to the Kyoto Encyclopedia of Genes and Genomes and the Biochemically, Genetically, and Genomically structured metabolic databases for a list of genes, and the enzymes they encode, that catalyze reactions in human cells. The Online Mendelian Inheritance in Man database provided the disorders associated with each gene. The authors constructed a network that linked diseases with mutated enzymes in adjacent pathways. Their grouping contained one “giant” cluster and several smaller ones, including purine and fatty acid metabolism, which constituted distinct, highly interlinked groups. Most diseases linked only to a few others, but certain diseases, such as hypertension, acted as “hubs.” The networks should aid researchers in identifying the metabolic origin of diseases, the authors say. — K.M.

“*The implications of human metabolic network topology for disease comorbidity*” by D.-S. Lee, J. Park, K. A. Kay, N. A. Christakis, Z. N. Oltvai, and A.-L. Barabási (see pages 9880–9885)

AGRICULTURAL SCIENCES

How rice accumulates arsenic

Arsenic poisoning is an endemic public health problem in Bangladesh and India, where arsenic exists in the groundwater and is also taken up by rice plants in paddies. In flooded rice paddies, arsenic(III), or arsenite, is the dominant chemical species. Jian Ma *et al.* identified two proteins that represent the major pathway of arsenite uptake in rice. An aquaporin, Lsi1, and an efflux carrier, Lsi2, function primarily as

silicic acid transporters but also allow passage of the similarly sized molecule, arsenous acid. Both proteins are expressed in the plant’s roots, but Lsi1 is the port of entry for arsenite, whereas Lsi2 controls flow from root tissue to the above-ground parts of the plant. The authors demonstrated Lsi1’s arsenite transport activity in *Xenopus* oocytes and yeast, showing that *lsi1* mutant rice plants were inhibited in arsenite uptake. Although the authors found it difficult to show transport by Lsi2 in cellular models, they showed that arsenic levels in the rice shoot and grain of two independent *lsi2* mutants were markedly reduced. Because silicic acid inhibits arsenite accumulation in rice shoots, the authors suggest that increasing available soil silicon may be a way to decrease the transfer of arsenic to the food chain. — K.M.



Arsenic-contaminated flooded rice paddy in West Bengal.

“*Transporters of arsenite in rice and their role in arsenic accumulation in rice grain*” by Jian Feng Ma, Naoki Yamaji, Namiki Mitani, Xiao-Yan Xu, Yu-Hong Su, Steve P. McGrath, and Fang-Jie Zhao (see pages 9931–9935)

GENETICS

Genetic variation reveals misclassifications

In nearly all known mammalian genomes, some members of a species have been found to have differing numbers of certain small genomic regions. In humans, this variability—called copy number variation (CNV)—has been linked to a susceptibility to diseases such as Alzheimer’s and Parkinson’s and to HIV-1 infection. John Marioni *et al.* developed a method for assessing the quality of genome-wide CNV data where family information is available. Information from parents and their offspring is used to estimate the frequency with which the CNV status of a region of interest differs on each inherited chromosome. This approach can also help to better characterize regions of CNV in the human genome. Marioni *et al.* examined CNV classifications made for individuals in the human HapMap haplotype

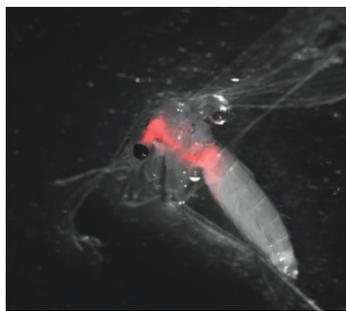
database and concluded that previous classifications had underestimated the number of regions where gene copy numbers increased. In some cases, the frequency of misclassification was as high as 50%. The authors say their findings should help to study CNV and its relationship to the pathogenesis of disease. — F.A.

“Hidden copy number variation in the HapMap population” by John C. Marioni, Michael White, Simon Tavaré, and Andrew G. Lynch (see pages 10067–10072)

MEDICAL SCIENCES

Infected sand flies can transmit thousands of parasites

Endemic to many tropical and subtropical countries, the disease Leishmaniasis causes severe boils on the skin of patients bitten by sand flies harboring the protozoan parasite *Leishmania ma-*



Sand fly infected with *Leishmania* parasites engineered to express red fluorescent protein.

major. Long-term infection with other *Leishmania* species can lead to fevers, anemia, and liver and spleen damage. The infectious dose transmitted by sand fly bites, however, was heretofore not known. Nicola Kimblin *et al.* developed a real-time PCR-based method for studying the transmission of parasites from infected sand flies to mice. The authors showed that the number of parasites passed on varied

widely, but fell into two general categories: three-fourths of the mice received a dose of <600 parasites, whereas the remaining animals received a dose of up to 100,000 potentially disease-causing cells. Mice infected with higher numbers of parasites quickly developed large lesions, which eventually healed. On the other hand, mice infected with a lower-dose inoculum displayed only minor lesions but frequently developed a chronic infection that established the host animal as a long-term reservoir of the parasite. This variation in infectious dose may be an important and overlooked determinant of disease outcome and may aid in

the development of a Leishmaniasis vaccine, according to the authors. — F.A.

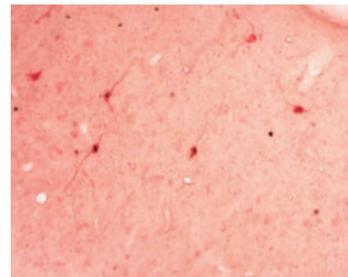
“Quantification of the infectious dose of *Leishmania major* transmitted to the skin by single sand flies” by Nicola Kimblin, Nathan Peters, Alain Debrabant, Nagila Secundino, Jackson Egen, Phillip Lawyer, Michael P. Fay, Shaden Kamhawi, and David Sacks (see pages 10125–10130)

NEUROSCIENCE

Sleep-activated neurons found in the cerebral cortex

Slow-wave activity (SWA) is a hallmark of brain activity during slow-wave sleep. Previous research has suggested that SWA is correlated with the recuperative properties of sleep and the brain’s ability to learn. Populations of neurons that are specifically activated during sleep have been identified in the basal forebrain and preoptic anterior hypothalamus. However, how the cortex is involved in the production of SWA has been a mystery.

Dmitry Gerashchenko *et al.* found that the cortex also harbors a collection of GABAergic interneurons that are activated during spontaneous sleep and during the “catch-up” sleep that occurs after sleep deprivation. The authors show that these GABAergic neurons express nitric oxide synthase (nNOS), and the fraction of these neurons that are sleep-active is correlated with a measure of SWA intensity known as “delta energy.” If nNOS neurons are found to be necessary for SWA generation, then loss or damage of these neurons may interfere with sleep regulation and have implications for learning and memory, the authors say. — B.P.T.



Sleep-activated neurons (in red) found in the cerebral cortex.

“Identification of a population of sleep-active cerebral cortex neurons” by Dmitry Gerashchenko, Jonathan P. Wisor, Deirdre Burns, Rebecca K. Reh, Priyattam J. Shiromani, Takeshi Sakurai, Horacio O. de la Iglesia, and Thomas S. Kilduff (see pages 10227–10232)