The combined benefits of exercise on the aged brain

Exercise may directly affect the brain or involve a myriad of tissues, including the liver, muscle, and adipose tissue. Horowitz et al. demonstrate that exercise-induced glycosylphosphatidylinositol-specific phospholipase D1 (GPLD1) from the liver mediates improved cognition in mice. GPLD1 hydrolyzes glycosylphosphatidylinositol (GPI) linkages that anchor proteins to membranes, releasing them into the circulation. Which proteins are released and how this connects with other exercise-induced factors is unknown.

...from skeletal muscle (9), liver hepatokines (10), fat-derived adipokines (11), exosomes (a type of extracellular vesicle) (12), and metabolites are altered. These factors may work not only directly on the brain but also, as exemplified in the work of Horowitz et al., through extensive tissue cross-talk. Because exercise has such complex effects, systems biology approaches will be necessary to unravel the intricacies of how exercise contributes to cognitive function (13).

Although hippocampal neurogenesis and behavioral outcomes were tested in mice by Horowitz et al., the increase of GPLD1 also needs to be tested against other hallmarks of brain aging, including neuroinflammation, synapse pruning, and neurophysiological deficits that have also been shown to cause age-associated cognitive decline (14). Studies using GPLD1 in mouse models of neurodegenerative disorders such as Alzheimer’s disease may also be warranted.

The observation that GPLD1 was increased in exercised mice as well as in physically active humans underlines the robustness of this finding and the potential for future translational studies. The ability to transfer the functional benefits of exercise through plasma adds to current interest in plasma rejuvenation as an intervention to delay or reverse aspects of the aging process. However, the safety and ethical concerns inherent in provision and access to plasma remain to be addressed. These findings also correspond to a prior report that showed the inverse—that the negative effects of age and peripheral muscle injury could be transferred between mice by plasma transfer (15). Generally, exercise is thought to prevent only age-associated changes, but an important insight from the study of Horowitz et al. is that exercise also has a rejuvenating effect. This emphasizes the importance of understanding how exercise has broad and advantageous effects on aging. Future studies will need to determine the intensity, duration, and frequency of exercise needed to engage these beneficial effects, particularly in humans. Whether these are acute effects of exercise or the result of chronic activity (the mice had running wheels for >40 days) is a central question to be answered. These findings, along with ongoing clinical studies, should help to provide the public with evidence-based knowledge to guide their own physical activity to promote healthy brain aging. 

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ACKNOWLEDGMENTS

Supported by NIH grants R01AG05943, R21AG062894, and P30AG050911 and by a Veterans Administration grant 10IBX003906.

10.1126/science.abc8830

VIEWPOINT: COVID-19

Rigorous wildlife disease surveillance

A decentralized model could address global health risks associated with wildlife exploitation

By Mrinalini Watsa and Wildlife Disease Surveillance Focus Group

Evidence suggests that zoonotic (animal origin) coronaviruses have caused three recent emerging infectious disease (EID) outbreaks: severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and the current coronavirus disease 2019 (COVID-19) pandemic. In the search for an intermediate host for SARS coronavirus 2 (SARS-CoV-2, which causes COVID-19), studies have identified SARS-CoV-2-like strains in bats (7) and pangolins (2), but these do not contain the same polybasic cleavage site that is present in SARS-CoV-2 (3). It is unknown what the intermediate host for this spillover event was because to date there are no international or national conventions on pathogen screening associated with animals, animal products, or their movements, and capacity for EID diagnostics is limited along much of the human-wildlife interface. EID risks associated with the wildlife trade remain the largest unmet challenge of current disease surveillance efforts.

Although viruses represent a fraction of ~1400 known human pathogens, they place a disproportionate burden on global health (4). Around 89% of the 180 recognized RNA viruses with the potential to harm humans are zoonotic. Coronaviruses are only the tip of the spillover iceberg: HIV came from nonhuman primates, Ebola came from bats, and H5N1 and H1N1 influenza strains came from birds and pigs, respectively. Indeed, 60% of EIDs are zoonotic in nature, and more than 70% of these have an origin in wildlife (5).

ACKNOWLEDGMENTS

Supported by NIH grants R01AG05943, R21AG062894, and P30AG050911 and by a Veterans Administration grant 10IBX003906.

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Published by AAAS

10 JULY 2020 • VOL 369 ISSUE 6500 145
Unchecked exploitation of wildlife—whether for sustenance or profit, legal or illegal—puts humans in direct contact with myriad unfamiliar species. Increased contact occurs in the global practice of bushmeat and game hunting and in wildlife farms, which often unsustainably and illegally supply wildlife for consumption or trade (6). Imported, hunted, and farmed wildlife then reach a common endpoint, wildlife markets. There, animals endure debilitating and immunocompromising conditions that promote disease transmission: packed cages, poor biosecurity, and unhygienic shedding of animal excreta (7). Direct human-wildlife contact, mixing of nonendemic wildlife species, and limited health and safety standards are all criteria for a zoonotic hotspot. Many wildlife markets around the world meet these criteria, yet disease surveillance in them is largely absent. More broadly, although the Convention on the International Trade in Endangered Species (CITES) regulates international wildlife trade on the basis of species’ endangered status, only a few countries use strict veterinary import controls, and there are no global regulations on pathogen screening associated with the international trade in wildlife.

Pathogen biosurveillance and how humans interact with wildlife are at the crux of EID risk management and response. After bats were identified as likely reservoirs for a range of zoonotic events (such as Hendra, Nipah, SARS, MERS, and Ebola) (8), surveillance of a single cave in southwest China between 2011 and 2015 revealed 11 novel coronaviruses (9). From 2015 to 2017, of 1497 people tested in the surrounding Yunnan, Guangxi, and Guangdong districts, nine (0.6%) were positive for prior bat coronavirus antibodies, and 265 (17%) reported SARS- or influenza-type symptoms associated with contact with poultry, carnivores, rodents, shrews, or bats (10). These findings, formally reported in September 2019, provided a warning about the risk of zoonotic coronaviruses that was neither heard nor heeded. The COVID-19 pandemic is evidence that bridging the gap between research and response is critical to anticipating and mitigating future spill-over events.

PREDICT, the intermittently federally funded offshoot of the 2009 United States Agency for International Development (USAID) Emerging Pandemic Threats program that partially financed the study of bat coronaviruses (10), screened 164,000 animals and humans and detected 949 novel viruses in zoonotic hotspots across 30 countries between 2009 and 2019. The Global Virome Project—a collaboration between experts in global health and pandemic prevention—aims to sequence all animal virus strains over a 10-year period, with a projected cost of $1.2 billion. Both projects share stakeholders, and although their missions are likely to adapt to a post–COVID-19 world, one of their stated goals includes strengthening existing laboratory capacities along the human-wildlife interface. But are there sufficient numbers of animal pathogen reference laboratories? According to the World Organisation for Animal Health (OIE) (11), there are 125 reference laboratories certified to screen for one or more target pathogens (and not for broad pathogen surveillance). Their global distribution does not reflect EID risks. Southeast Asia, Africa, and Central and South America carry the burden of EID risk, yet 78 (62%) of reference laboratories are in Europe and North America; only 33 (26%) are in Asia (14 in China and 8 in Japan), with 12 (34%) spread between 7 countries; 3 (~2%) are in Africa; 4 (~3%) are in Australia, and 8 (~6%) are in South America. Although this does not account for laboratory size or screening methods and capacity, it is evident that many regions with zoonotic hotspots lack testing facilities with the capability of conducting disease surveillance.

What can be done to mitigate future zoonotic EIDs? Centralized biosurveillance efforts produce results but are expensive, maintained by a select few countries, and subject to political whims, as evidenced by the 2019 shift in funding for PREDICT, a recent recall of U.S. National Institutes of Health (NIH) support for the EcoHealth Alliance, and the withdrawal of the United States from the World Health Organization (WHO). As such, they are not immediately scalable, nor do they stimulate widespread capacity. The international wildlife trade is a substantial global industry in need of greater oversight. Because ill-conceived restrictions would affect millions of people and likely drive these activities deeper underground, further impeding regulation (12), the first step is to establish a more cost-effective, decentralized disease surveillance system. It would empower local wildlife and public health professionals to test for diseases year round, at source, without criminalizing public participation in screening programs. Such screening was not technologically feasible after the emergence of the H1N1 influenza virus in 2009, but now, affordable modern technologies enable quick in situ biosample processing, whole-genome sequencing, metagenomics, and metabolomics of pathogens. This would enable proactive, broad, routine wildlife pathogen screening in remote areas rather than reactive targeted testing.

Decentralized laboratories must be able to extract genomic material and conduct metagenomic sequencing and targeted pathogen testing if necessary. As demand increases, individual technologies have evolved to be smaller, simpler, and more affordable. Multiplex polymerase chain re-
Markets selling live animals, including wildlife such as this slow loris at the Borito Market in Jakarta, Indonesia, are hotspots for zoonotic spillovers and should be monitored to better manage emerging infectious diseases.

of this uncertainty, allowing molecular epidemiology to inform short- and long-term responses on both a local and global level.

To complement decentralized laboratories, a publicly accessible, centralized, curated system for monitoring pathogens must be established for three main reasons: (i) This would provide instant pathogen classifications based on comparative genomics, further cross-linked to reference data on prevalence by species and region. (ii) A centralized curated system could alert to EID indicators, including gains and losses of strains, pathogen-specific changes in host species numbers, rapid increases in mutation rates that may indicate pathogen spillover into a naïve host, and pathogen detection in traded animals that do not occur in wild counterparts. (iii) For virus families that are poised to spillover into human populations, genomic sequence data can reveal diversity of key pathogen proteins in circulating strains (for example, the spike protein that mediates human cell entry of coronaviruses, and the RNA-dependent RNA polymerase that is important for viral replication). Such approaches assist in identifying broad-spectrum antivirals and vaccination targets as well as treatment-resistant pathogen variants that pose a risk of generating future EIDs.

An example of a disease-focused public database that could be expanded is the GISAID (global initiative on sharing all influenza data) EpiFlu repository, a global initiative developed for sharing influenza virus sequence data and currently also documenting SARS-CoV-2 sequences. It facilitates data access for registered users while securing data ownership by requiring that contributors be acknowledged in derivative research. Additionally, the database could include report-generating features such as those in the Zoological Information Management Software (ZIMS), used by more than 1000 Species360–accredited zoological institutions worldwide to upload biomedical data and compute reference ranges across multiple variables and species.

An internationally recognized standard for managing wildlife trade on the basis of known disease risks should be established. Currently, few countries consider disease risk as a factor in regulating wildlife imports and exports, and a disease status equivalent to CITES is lacking. Pathogen screening is also not required nor facilitated before, during, or after translocating wildlife products, leaving pathogen status to be declared by the shipper, who may not have the experience to make such determinations. Because a large number of animals naturally carry pathogens that could spillover to humans if improperly handled, the means to identify the species for which security standards should be enhanced, or for which trade and consumption should potentially be prohibited, is needed. An important caveat is that such classifications can stigmatize animals to their detriment and incite fear-based human behaviors that may threaten species conservation.

A decentralized network could improve feedback between those who screen samples and those who curate data to bolster the safety of wildlife and humans, fundamentally “One Health” approach. This would increase localized knowledge of EID risks, provide earlier warnings and faster global responses to spillovers, and inform wildlife trade policy. This model is more robust to shifting political landscapes and funding and does not ignore the role of advanced regional research laboratories, which also provide vital targeted pathogen screening. Research laboratories can also provide samples for or generate high-quality host de novo reference genome assemblies and expand regional capacity for biobanking, including cell cultures, which will improve understanding of the co-evolutionary processes that underlie pathogen-host range and susceptibility. By giving more parties a stake in the effort, decentralization is more likely to succeed in garnering geographically representative participation that explicitly includes the most at-risk, under-resourced regions.

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SUPPLEMENTARY MATERIALS
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10.1126/science.abc0017

Published by AAAS
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Science 369 (6500), 145-147.
DOI: 10.1126/science.abc0017