Writing in *The Conversation*, Linda-Gail Bekker cautions that: “PrEP is not the only prevention tool. PrEP should be provided alongside HIV self-testing, access to condoms, screening and treatment for sexually transmitted infections and access to contraception for women of childbearing potential.”

Unintended consequences of relying too much on one measure could diminish the breakthrough success that now appears within reach. They could also shift the economic burden of AIDS that poorer countries have to carry to other diseases. One could also imagine that, as soon as the prevalence of HIV infections has been rolled back significantly, the motivation to get a Lenacapavir injection every six months could decline as well. The result could be an equilibrium at a lower level, which could allow the AIDS epidemic to persist for many years to come. For these reasons, a vaccine offering permanent protection would be a preferable solution, but the road to its development has proven to be arduous.

Vaccine efforts

The rapid development of several effective vaccines against SARS-CoV-2 within less than 12 months has helped to rein in the COVID-19 pandemic (Curr. Biol. (2021) *31*, R101–R103). Unfortunately, HIV resides at the opposite side of the scale for vaccine development speed — after 40 years, there is still no vaccine that offers a degree of protection that would be practically useful. The best efforts so far have only protected a fraction of participants for a limited time. Therefore, no vaccine has been approved for introduction yet. One fundamental problem that has made vaccine development difficult is the fact that the virus can mutate rapidly and thus evade the immune response triggered by a given vaccine.

One strategy to counter this vaccine evasion is to induce broadly neutralising antibodies by the germline-targeting approach. The vaccination targets naive B cells from which the plasma cells producing the desired antibodies will develop. William Schief and colleagues at Scripps Research in San Diego, USA and at IAVI (a global non-profit organisation launched in 1996 as the International AIDS Vaccine Initiative) are pursuing this route and have published a series of four papers on preclinical studies in *Science* and in its sister journals in May 2024, which Rogier Sanders and John Moore discussed in a perspective article (Science (2024) *384*, 738–739). “All in all, these studies show that we have a good chance at creating an effective HIV vaccine — we just need to keep iterating and build on these findings in future clinical trials,” Schief concludes.

In a separate effort, Sachin Bhagchandani at the Massachusetts Institute of Technology, USA and colleagues have developed methods to avoid the development of vaccine-resistant viruses by spreading out the vaccine dose over several time points, for instance every other day for two weeks. This protocol, called escalating dose immunisation, is meant to mimic the natural exposure of the body to a growing population of viruses, which induces the immune system to ramp up its defences accordingly. Initially, the researchers showed that a series of seven vaccinations with increasing doses yields an improved immune response. As this schedule is too complex for mass vaccinations, they went on to look for simpler patterns producing the same effect. In September 2024 they reported animal experiments showing that two vaccinations with a protein subunit given seven days apart also trigger the desired immune response, if 20% of the total dose is given the first time and the remaining 80% the second time (Sci. Immunol. (2024) *9*, adl3755). The researchers found that the two-dose split produced a five-fold improvement in the T-cell response and a 60-fold increase in antibody count.

The quest for a vaccine with convincing clinically proven effects continues. Soon, the widespread availability of a virtually 100% effective prophylactic treatment will make it harder for researchers to justify clinical trials. They would have to be quite confident of the exceptionally good protection of their vaccine candidate to test it against Lenacapavir. Thus, the prophylactic injection looks set to remain the best option in the fight against AIDS for some time.

Michael Gross is a science writer based at Oxford. He can be contacted via his web page at www.michaelgross.co.uk

Obituary

Harvey J. Karten (1935–2024)

Thomas E. Finger

Harvey J. Karten, the pre-eminent comparative neuroscientist of this era, died on July 15 of this year, two days after his 89th birthday. ‘Harvey’, as friends, students, and colleagues alike knew him, was most recognized for his landmark studies that fundamentally reshaped our concepts of brain organization and intelligence in non-mammalian vertebrates, especially birds.

While his groundbreaking work in avian neuroscience stands as his most recognized achievement, Harvey’s contributions to the field of systems neuroscience were far-reaching, including seminal findings about the visual, auditory, trigeminal, and viscerosensory modalities as well as organization of the basal ganglia. The impact of his work was acknowledged at the highest levels, earning Harvey election to the American Academy of Arts and Sciences in 2008 and to the National Academy of Sciences in 2015.

Harvey’s scientific passion was driven by three great loves: evolutionary biology, photographic images, and laminated neural structures. One of Harvey’s favorite quotes was from Theodosius Dobzhansky: “nothing in biology makes sense except in the light of evolution”. Harvey’s wide-ranging interests were not confined to specific systems or organisms, with publications spanning an array of species, from leeches and lobsters to squirrels and squirrel monkeys.

Harvey’s interest in evolutionary neurobiology led him to work with John Hildebrand (University of Arizona) in 1999 to create the Gordon Research Conference on Neurobiology. Hildebrand described Harvey’s contributions as so:

> “Karten’s career is a story of intellectual courage. His early development of insights about the evolution of the vertebrate forebrain seriously challenged what then was ossified academic opinion. One

Harvey Karten (2019): Photo courtesy of Betsy Heafitz.

broadly maintained tenet regarded the evolution of the human forebrain as having come about by a gradual forward migration of "primitive" brainstem functions, the incorporation of which led to endowment of the human cortex with its higher cognitive centers and hence abilities. That such a theory was so broadly accepted by the mid-century's neurological establishment, despite the absence of comparative studies that might have suggested how such transformations could have occurred, must have struck a young and highly intelligent neuroanatomist as bizarrely irresponsible. Throughout his career, Karten's research has challenged ingrained orthodoxies. This has demanded of him great persistence, requiring resolute intellectual and emotional strength while his work has been repeatedly attacked. Karten's brilliant clarification of the evolutionary basis of mammalian forebrain organization and his demonstration, through detailed analyses, of the correspondences between the avian and mammalian brain *in toto* — a rare example of a total paradigm shift in our understanding divergent brain evolution — exemplify his meticulous and deliberate approach to neuroanatomical analyses."

Harvey grew up attending traditional Jewish boarding schools, or yeshivas, in New York City. Although Harvey was not receptive to the subject matter, the rigorous training likely proved useful in his mastery of the early works in comparative neuroanatomy. His academic path led him to Yeshiva College, where he graduated in 1955, before he continued on to medical school at the Albert Einstein School of Medicine.

Upon completing his studies at Albert Einstein, Harvey's career took him westward, which fostered his love of skiing and outdoors adventure. He undertook an internship in Salt Lake City followed by a residency in psychiatry in Colorado. However, Harvey's scientific curiosity led him to abandon the residency part way through to join a research position at the Walter Reed Army Institute of Research in Washington, D.C. There he apprenticed under the direction of Walle Nauta, a pre-eminent neuroscientist from the Netherlands who was famous for the development of methods for silver-staining of degenerating axons for delineating connections within the brain. This technique was most useful when coupled with the placement of accurate and reproducible lesions using a reliable stereotaxic system, as had been done in various mammalian systems (e.g.[1,2]). Driven by his interest in brain evolution, Harvey chose to focus on the pigeon as a new model. This relatively unspecialized avian species was an ideal choice, given the extensive history of behavioral studies on this species, including early research on visual function co-authored by Harvey and his Walter Reed colleague William (Bill) Hodos. Pigeons were also readily available in standard form from breeders.

In a close collaboration, Harvey and Bill Hodos generated a meticulously documented stereotaxic atlas for the pigeon[3]. This endeavor required developing both a high-quality, stable head-holder and a high-resolution imaging arrangement to allow adequate documentation of cell groups in a relatively small brain. In keeping with his life-long pursuit of high-quality images, Harvey utilized a six-foot-long (approximately 2 m) horizontal optical bench system from Bausch and Lomb. This system projected the image of a microscope slide onto a camera back for 8" x 10" (20 x 25 cm) cut sheet film. This allowed for flat-field magnification factors of 12x to 25x across the entire section while maintaining a resolution roughly equivalent to 1,000 megapixels in today's terms. These plates were reproduced at essentially full magnification in the brain atlas.

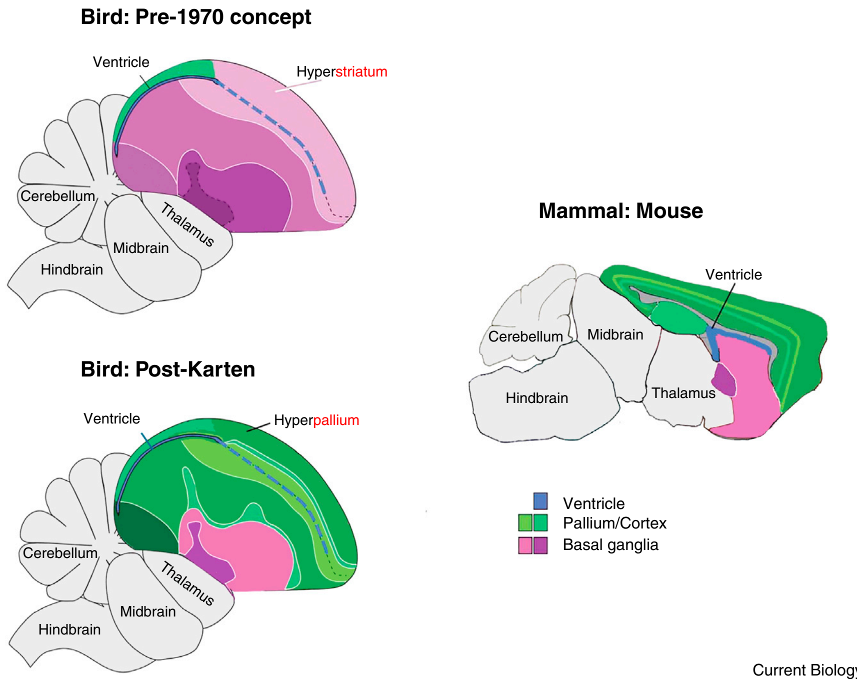
By the time that the brain atlas had been published (1967), Harvey and his mentor, Walle Nauta, had moved to MIT, where Harvey assumed the position of Research Associate within Nauta's research group, which then included Lennart Heimer, who had joined in 1965. At that time, this formidable trio were among the foremost neuroanatomists in the world. At MIT, these investigators also had frequent interactions with others in the Boston neuroscience community including Jerome Lettvin, Pasko Rakic, Sanford Palay, David Hubel, and Torsten Wiesel.

In 1974, following a nine-year stay as a Research Associate and Senior Research Scientist at MIT, Harvey joined the faculty at SUNY Stony Brook as a Professor of Psychiatry and Behavioral Science. In 1986, Harvey left Stony Brook to join the faculty at the University of California San Diego (UCSD) as a Professor of Neurosciences and as Adjunct Professor at the nearby Salk Institute. In 2004, Harvey was named Distinguished Professor at UCSD and transitioned to Emeritus status in 2014, although he continued with collaborative research, his last co-authored paper being published just two months before his death[4].

The brain atlas was not just a technical tour de force but also provided the platform for Harvey's landmark studies on sensory pathways and forebrain organization of the pigeon. In the years following the move to MIT, Harvey published a series of papers detailing sensory lemniscal pathways in the brain of the pigeon, leading to the seminal papers postulating a new conceptualization on the organization of the telencephalon of non-mammalian vertebrates[5,6]. At this time, the orthodox view based on the classic comparative studies of Ariëns Kappers and others[7] was that the six-layered neocortex was a mammalian invention that had accreted onto a pre-existing primitive non-laminated network of the basal ganglia present in birds and reptiles. Hence the various areas of the telencephalon of birds were given names ending in the root term ‘striatum’ to designate the basal ganglia-like nature of these structures.

This conceptualization led to the then popular ‘triune brain’ hypothesis of Paul D. MacLean[8]. This posits that the mammalian brain consists of three principal parts with later parts being added onto a pre-existing ‘reptilian complex’, as found in the forebrains of birds and reptiles, and equivalent to the basal ganglia of mammals. Subsequently, or so the theory went, early mammals added on the limbic system (paleomammalian complex, e.g. amygdala and hippocampus), with the last evolutionary addition being the neomammalian complex (six-layer neocortex), which underlays higher-order thinking and complex sensory function. Harvey’s contrasting formulation, based on his studies showing discrete sensory pathways targeting specific subnuclei within the avian forebrain, predicted that, although the bird telencephalon lacked a six-layered neocortex, it did possess restricted cell groups that received specific sensory information and that formed connections within the forebrain that were equivalent to the connectivity occurring in the six-layered neocortex. In other words, the essential circuitry and processing capabilities of the neocortex were indeed present within the avian forebrain, but they just were not organized into a layered structure. Further, application of then novel histochemical techniques allowed demonstration that only limited basal regions of the avian forebrain had chemical features similar to those of the mammalian basal ganglia. These crucial insights then launched investigations into the cognitive abilities of birds, which we now know to rival those of mammals. The six-layered organization of the mammalian neocortex was proven unnecessary for computational capabilities as long as the underlying connectivity and computational units were present in other forms.

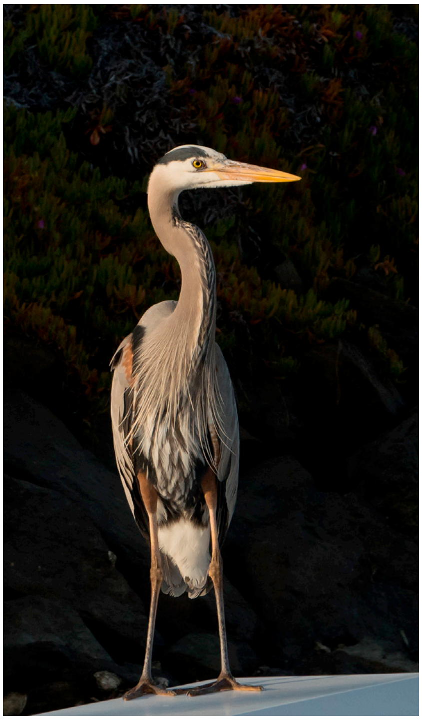
In 2002, in recognition of Harvey’s insights into the nature of these non-laminated but cortex-like nuclei in the brains of birds, the Avian Brain Nomenclature Forum, organized by Anton Reiner and Erich D. Jarvis, generated a new nomenclature for brain structures in birds, often replacing the term ‘striatum’ for the non-striatal centers and replacing it with ‘pallium’; for example, ‘hyperstriatum’ became ‘hyperpallium’[9,10].



Semi-schematic drawings showing the revolutionary conceptual change brought about by the works of Harvey Karten: Prior to Harvey’s studies (pre-1970), the forebrain of birds was considered largely equivalent to the basal ganglia of mammals and therefore capable of driving only reflexive behaviors. In a series of studies spanning decades, Harvey showed that the bulk of the forebrain of birds contains neuronal systems equivalent to the mammalian cortex and capable of complex cognitive tasks. Purple shades denote basal ganglia structures; green shows neocortex or cortex-equivalent cell groups. (Modified from[21].)

A second long-term major research effort of Harvey’s related to the multiplicity of visual processing streams. This effort began in the late 1960s, when the main interest in visual neuroscience related to the landmark series of papers by Hubel and Wiesel describing the processing of information in the geniculostriate system targeting the visual cortex (1963–1968). The visual system of birds was considered to be dominated by the optic tectum rather than the cortex. Harvey ultimately found[11] a projection system in pigeons and owls like the geniculostriate system targeting the dorsal thalamus and ultimately the visual wulst, which he likened to the visual cortex. In addition, Harvey noted a multiplicity of retinal targets within the diencephalon, leading to a series of papers describing the then little-known basal optic nuclei and their role in directing eye movement[12–14]. These seminal studies revealed a unique subset of retinal ganglion cells, displaced ganglion cells, which projected uniquely to the basal optic nuclei that were presynaptic to cerebellar areas involved in gaze control. These studies led Harvey to the retina, one of his favorite laminated structures. Harvey’s adoption of the relatively new immunocytochemical techniques then allowed for rigorous anatomical dissection of numerous retinal subcircuits and cell types.

Harvey’s broad interests in nature and many professional friendships led him to become involved in diverse projects outside his main focus on birds. For example, his first two graduate students, Len Maler and myself, ended up studying fish. Despite this shift of vertebrate clade, Harvey was immensely supportive of both of us. Len Maler started out



Great blue heron: Taken by Harvey Karten (March 2021).

with a bird project but then became entranced with a lecture by Michael V.L. Bennett in which he described the active electrosensory system of the elephant-nosed mormyrid teleost *Gnathonemus petersii*. Once the project was described to Harvey, along with the requisite images of the huge cerebellum (the largest of any vertebrate!) and beautifully layered lateral line lobe, he was all in. In fact, he became so enthusiastic about electric fish that he arranged to take us on his six-month sabbatical with Theodore Holmes Bullock at the Scripps Institution of Oceanography in San Diego.

Similarly, work with Phil Zeigler on trigeminal pathways and feeding behavior in pigeons[15,16] led to uncovering a fallacy in the then current formulation of the ‘lateral hypothalamic syndrome’. This ‘syndrome’, which appeared following large lesions of the lateral hypothalamus, included a component of ipsilateral orosensory neglect[17] along with dysphagia, adipsia, and weight loss. Zeigler and Karten noticed that lesions of the central trigeminal nuclei and pathways in pigeons recapitulated the orosensory neglect, adipsia, and aphagia components of the lateral hypothalamic syndrome and showed that these deficits occur with the lesion of the central trigeminal lemniscus, i.e. the central pathway conveying orosensory information toward the forebrain[18]. Harvey’s interest in trigeminal systems continued sporadically throughout his publishing career, including a series of recent works in rodents undertaken with David Kleinfeld during Harvey’s years in ‘retirement’[19,20].

Throughout his life, Harvey was an avid outdoorsman, participating in diverse activities including downhill skiing, hiking, and sailing. Indeed, Harvey became somewhat of an internet guru for the maintenance of the Tayana 37 sailboat, which he owned. In his retirement years, Harvey took his mirrorless, digital camera to the nearby marshes to photograph his beloved birds. His photos were striking in composition and detail and typify his approach to images, whether they be scientific or personal.

DECLARATION OF INTERESTS

The author declares no competing interests.

REFERENCES

1. Olszewski, J. (1952). The Thalamus of the Macaca Mulatta (Basel: Karger Publishers), pp. 7b–13.
2. Horsley, V.A.H., and Clarke, R.H. (1908). The Structure and Functions of the Cerebellum Examined by a New Method (London: J. Bale, Sons and Danielsson).
3. Karten, H.J., and Hodos, W. (1967). A Stereotaxic Atlas of the Brain of the Pigeon (*Columba Livia*), Volume 696 (Baltimore, MD: Johns Hopkins Press).
4. Reiner, A., Medina, L., Abellan, A., Deng, Y., Toledo, C.A.B., Luksch, H., Vega-Zuniga, T., Riley, N.B., Hodos, W., and Karten, H.J. (2024). Neurochemistry and circuit organization of the lateral spiriform nucleus of birds: A uniquely nonmammalian direct pathway component of the basal ganglia. J. Comp. Neurol. *532*, e25620. https://doi.org/10.1002/cne.25620.
5. Karten, H.J. (1969). The organization of the avian telencephalon and some speculations on the phylogeny of the amniote telencephalon. Ann. N. Y. Acad. Sci. *167*, 164–179.
6. Nauta, W.J.H., and Karten, H.J. (1970). A general profile of the vertebrate brain, with sidelights on the ancestry of cerebral cortex. In The Neurosciences: Second Study Program, F.O. Schmitt and F.G. Worden, eds. (New York, NY: Rockefeller University Press), pp. 7–26.
7. Ariëns Kappers, C.U., Huber, G.C., and Crosby, E.C. (1936). The Comparative Anatomy of the Nervous System of Vertebrates Including Man, 2nd edition, 2 volumes (New York, NY: Macmillan).
8. MacLean, P.D. (1988). Triune Brain. In Comparative Neuroscience and Neurobiology, L.N. Irwin, ed. (Boston, MA: Birkhäuser), pp. 126–128.
9. Reiner, A., Perkel, D.J., Bruce, L.L., Butler, A.B., Csillag, A., Kuenzel, W., Medina, L., Paxinos, G., Shimizu, T., Striedter, G., *et al*. (2004). Revised nomenclature for avian telencephalon and some related brainstem nuclei. J. Comp. Neurol. *473*, 377–414. https://doi.org/10.1002/cne.20118.
10. Jarvis, E.D., Güntürkün, O., Bruce, L., Csillag, A., Karten, H., Kuenzel, W., Medina, L., Paxinos, G., Perkel, P.J., Shimizu. T., *et al*. (2005). Avian brains and a new understanding of vertebrate brain evolution. Nat. Rev. Neurosci. *6*, 151–159. https://doi.org/10.1038/nrn1606.
11. Karten, H.J., Hodos, W., Nauta, W.J.H., and Revzin, A.M. (1973). Neural connections of the “visual wulst” of the avian telencephalon. Experimental studies in the pigeon (*Columba livia*) and owl (*Speotyto cunicularia*). J. Comp. Neurol. *150*, 253–277. https://doi.org/10.1002/cne.901500303.
12. Brecha, N., and Karten, H.J. (1979). Accessory optic projections upon oculomotor nuclei and vestibulocerebellum. Science *203*, 913–916. https://doi.org/10.1126/science.570303.
13. Fite, K.V., Brecha, N., Karten, H.J., and Hunt, S.P. (1981). Displaced ganglion cells and the accessory optic system of pigeon. J. Comp. Neurol. *195*, 279–288. https://doi.org/10.1002/cne.901950208.
14. Reiner, A., Brecha, N., and Karten, H.J. (1979). A specific projection of retinal displaced ganglion cells to the nucleus of the basal optic root in the chicken. Neuroscience *4*, 1679–1688. https://doi.org/10.1016/0306-4522(79)90027-7.
15. Zeigler, H.P., and Karten, H.J. (1973). Brain mechanisms and feeding behavior in the pigeon (*Columba livia*). II. Analysis of feeding behavior deficits after lesions of quinto-frontal structures. J. Comp. Neurol. *152*, 83–102. https://doi.org/10.1002/cne.901520106.
16. Zeigler, H.P., and Karten, H.J. (1973). Brain mechanisms and feeding behavior in the pigeon (Columba livia). I. Quinto-frontal structures. J. Comp. Neurol. 152, 59–81. https://doi.org/10.1002/cne.901520105.
17. Marshall, J.F., Turner, B.H., and Teitelbaum, P. (1971). Sensory neglect produced by lateral hypothalamic damage. Science *174*, 523–525. https://doi.org/10.1126/science.174.4008.523.
18. Zeigler, H.P., and Karten, H.J. (1974). Central trigeminal structures and the lateral hypothalamic syndrome in the rat. Science *186*, 636–638. https://doi.org/10.1126/science.186.4164.636.
19. McElvain, L.E., Friedman, B., Karten, H.J., Svoboda, K., Wang, F., Deschênes, M., and Kleinfeld, D. (2018). Circuits in the rodent brainstem that control whisking in concert with other orofacial motor actions. Neuroscience *368*, 152–170. https://doi.org/10.1016/j.neuroscience.2017.08.034.
20. Mercer Lindsay, N., Knutsen, P.M., Lozada, A.F., Gibbs, D., Karten, H.J., and Kleinfeld, D. (2019). Orofacial movements involve parallel corticobulbar projections from motor cortex to trigeminal premotor nuclei. Neuron *104*, 765–780.e3. https://doi.org/10.1016/j.neuron.2019.08.032.
21. Finger, T.E., Yamamoto, N., Karten, H.J., and Hof, P.R. (2013). Evolution of the forebrain — revisiting the pallium. J. Comp. Neurol. *521*, 3601–3603. https://doi.org/10.1002/cne.23444.

Rocky Mountain Taste and Smell Center, and Department of Cell and Developmental Biology, University of Colorado School of Medicine, 12801 East 17th Avenue, Aurora, CO 80045, USA.
E-mail: tom.finger@cuanschutz.edu