Renowned Skull Base Neurosurgeon Returns to His Stomping Grounds at UCSF

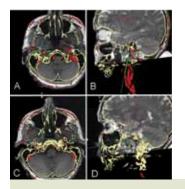
According to Dr. Philip

Theodosopoulos, this is an exciting time to be a skull base neurosurgeon. In the past, many lesions of the skull base could only be accessed through large, transfacial operations that left patients with significant disfigurement and morbidity. "But that has changed tremendously," he says. "We now have the instrumentation and experience to tackle almost anything in the skull base safely and with minimal morbidity."

After 10 years pioneering minimally invasive skull base surgery at the University of Cincinnati, Dr. Theodosopoulos has returned to UCSF, where he was a resident in the Department of Neurological Surgery, to lead the Skull Base Tumor Program. He is a leading figure in the movement away from invasive, open procedures towards treatment plans that combine smaller incisions, improved adjuvant therapies, new surgical technologies, and good clinical judgment that focuses on patient preferences and quality of life.

"We are thrilled to have him back as part of our team," says Dr. Michael McDermott, professor

Surgical plan for endoscopic removal of a schwannoma. Image courtesy of Ivan El-Sayed MD.



of neurological surgery and codirector of UCSF's Gamma Knife Radiosurgery Program. "He was the best resident we ever trained – all of our residents are highly skilled, but Dr. Theodosopoulos has an innate technical finesse."

Technical skill is especially important when skull base lesions are in close proximity to critical nerves and blood vessels. Acoustic neuromas, for example, are generally considered benign but often involve the nerves responsible for hearing and facial movements. Aggressively removing the tumors or irradiating them may halt growth for a time, but can cause hearing loss or facial nerve palsy - both devastating outcomes for patients. "We are now really focused on functional preservation for patients with these kinds of tumors," says Dr. Theodosopoulos. That may mean leaving a small part of the tumor behind or simply watching it with serial imaging to ensure a good quality of life for patients.

Chordoma is another tumor type for which the treatment paradigm has shifted, mainly as a result of surgical advances. Chordomas are slow growing but malignant, and patients may undergo three to four surgeries for recurrence, causing increasing morbidity and cosmetic disfigurement. Now many chordomas can be removed via an endoscopic endonasal procedure that does not require facial incisions.

For the past decade, Dr. Theodosopoulos has been at the forefront of developing endoscopic techniques to access pathologies of the skull base. Although he performed a cerebrovascular and skull base fellowship at Brigham and Women's Hospital from 2002-03, he did not hold his first endoscope until 2004. "When minimally invasive skull base surgery first came on the scene, I was a skeptic," he admits. "But there is no question that it has significantly improved outcomes for patients."

Since 2005, he has performed more than 500 fully endoscopic cases for skull base tumors and keeps pushing the envelope. This experience makes him uniquely at home in the Minimally Invasive Skull Base Surgery Center at UCSF. Co-directed by neurosurgeon Manish Aghi MD, PhD and otolaryngologist Ivan El-Sayed MD, the Center is devoted entirely to providing safe and effective minimally invasive treatment options for complex lesions of the paranasal sinuses and skull base.¹

"When I look at the first endoscopes we used it is like looking back at Neanderthal times," he says. "The instrumentation we have now is much more sophisticated, but we still have a long way to go."

Technical advances for endoscopic neurosurgery are the focus of the new Skull Base and Cerebrovascular Laboratory – a collaboration between the Neurological Surgery and Otolaryngology – Head and Neck Surgery (OHNS) Departments at UCSF. Directed by surgical anatomist Arnau Benet MD, the state-of-theart laboratory provides a surgical simulator and 3D neuroimaging

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Neurological Surgery

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Phone: 415/353-7500 Fax: 415/353-2889 http://neurosurgery.ucsf.edu <u>looking to the future</u>

The Brain Tumor Research Center (BTRC) at UCSF is made up of 23 laboratories devoted to studying the underpinnings of brain cancer. How does it form? How does it change when exposed to therapies? Who is at risk? From innovations in genome sequencing to the intricacies of cellsignaling pathways, the investigators at the BTRC each have a specialized niche and bring a unique viewpoint to tackling the problem of brain tumors.

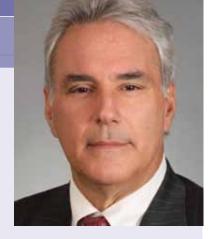
But while these individuals continuously make important contributions to their own fields of interest, the real strength of the BTRC lies in our collaborative research programs that involve multiple labs and bridge basic science and clinical research problems.

In 1973, the BTRC was founded on the concept of translational research, and it has since been built up through two key funding programs consistently awarded to us by the National Institutes of Health: the Program Project Grant (PPG) and the Specialized Program of Research Excellence (SPORE) for Brain Tumors. These highly competitive awards fund tightly integrated projects performed by teams of investigators in synergistic research environments. This year, the BTRC was awarded a new cycle of funding for both of these programs to continue its work.

The first PPG was awarded to BTRC investigators in 1979 to investigate the biology and therapy of malignant brain tumors, and the BTRC has been a recipient of SPORE funding since it first became available for brain tumor research in 2002. Since then, UCSF's infrastructure for performing large, ambitious projects has grown tremendously and the projects of 2013 are at the cutting edge of scientific research in this field.

The current PPG program is lead by Director of Neuro-Oncology. Susan Chang MD, and focuses on integrating imaging and tissue correlates to optimize the management of gliomas. Results from the previous PPG identified physiological imaging parameters for characterizing newly diagnosed and post-treatment GBM, which could be linked to ex vivo metabolic profiles and histological characteristics. In the current research program, we aim to translate those findings into clinical use, as well as obtain the first hyperpolarized carbon-13 metabolic imaging data from patients with brain tumors. This is an exciting new technology that can be used to monitor pyruvate metabolism and may serve as a useful biomarker of drug delivery and response to therapy. The final goal of the PPG will be to evaluate imaging and tissue parameters of newly diagnosed and post-treated GBM with specific emphasis on the genomic features of tumor heterogeneity and evolution.

Our SPORE program for this cycle will be the first brain tumor SPORE to include a project for pediatric brain tumors, focused on developing effective therapies for pediatric tumors with BRAF mutations. The remaining three projects of the SPORE program will continue the successes of the previous funding cycle: identifying genetic variations



associated with increased survival in low-grade glioma; combining genomic, physiological imaging, and histological data from lowgrade gliomas to identify causes of malignant transformation; and improving immunotherapy for brain cancer by combining a heat shock protein vaccine with inhibitors of an aberrant cell-signaling pathway.

I am confident that the work being done in these research programs will give us new tools for fighting brain tumors. As always, our goal at the BTRC is not only to advance scientific knowledge, but also to solve problems of real significance to patients.

Mitchel S. Berger MD Berthold and Belle N. Guggenhime Professor and Chair

Director, Brain Tumor Research Center

Department of Neurological Surgery, UCSF



Minimally invasive endoscopic approaches can now be safely and effectively used to access tumors of the paranasal sinuses and skull base.



3D reformation of CT scans showing normal anatomy of the skull base. Image courtesy of Christine Glastonbury MD.

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for optimizing routes to the clivus, infratemporal fossa, foramen magnum, paranasal sinuses, and intracranial lesions, as well as exploring novel approaches.

Developments in surgical approaches and tools have been particularly important in readdressing the problem of malignant skull base tumors. Combined with improvements in neo-adjuvant treatments, new technologies are giving skull base neurosurgeons an opportunity to remove lesions that were previously inoperable or carried a poor prognosis. Administering chemotherapy or radiation therapy before surgery, for example, may shrink the tumor enough to allow neurosurgeons to use smaller incisions or even endoscopic procedures to remove it, giving patients better outcomes.

These malignant tumors are often extremely complex and require input from a variety of specialists to design combination treatment plans. Drs. McDermott and Theodosopoulos lead a multidisciplinary skull base tumor board to regularly review complicated cases with their colleagues in Neuroradiology, Plastic Surgery, Radiation Oncology, Neuro-Otology, Neuro-Oncology, and OHNS. Dr. Theodosopoulos has ambitious plans for expanding UCSF's skull base research program as well. "One of the big attractions for me to come back to San Francisco was the ability to collaborate with basic scientists," he says "I think that is unique to UCSF – there is an effective collaborative effort to translate scientific discoveries to the clinical field."

While endoscopic surgery has revolutionized treatment for tumors like chordoma, there are still no effective medical treatments available. Scientists at the Brain Tumor Research Center have recently partnered with the Chordoma Foundation to establish a human chordoma xenograft that can be used to study the behavior of these tumors and to test new and existing therapies against them. This type of preclinical model will be essential to changing the poor track record of drug development in this area of neuro-oncology.

There have been few clinical trials of agents against any type of skull base tumor. This includes meningioma, despite the fact that it is the most frequently reported brain tumor histology, with an annual incidence of 7.10 per 100,000 individuals.² Brain

Tumor Research Center investigators are now looking to participate in the first multi-center trial of an mTOR inhibitor to treat meningioma.

But while pharmaceutical innovations have lagged behind, UCSF's large clinical experience with meningiomas has allowed for a series of retrospective outcome studies to refine existing treatment paradigms. One of these studies, funded in part by the nonprofit group Meningioma Mommas, provides evidence for selecting out less aggressive meningiomas based on anatomic location.3 "Patients with those types of tumors may benefit from subtotal resection to preserve function of critical structures," says Dr. McDermott. "Then we can follow up with radiosurgery to target any residual disease."

With new leadership, the skull base team at UCSF is ramping up its clinical and research capabilities, always with the goal of providing exceptional patient care. The new outlook is focused on prospective primary data collection, functional outcome determination, novel treatment schemata, and multimodality treatment.

1. For more information about the Minimally Invasive Skull Base Surgery Center at UCSF, visit: misb.ucsf.edu 2. Therese A. Dolecek, Jennifer M. Propp, Nancy E. Stroup, and Carol Kruchko. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2005–2009. **Neuro-Oncology** 2012;14(suppl 5):v1-49. 3. Kane AJ, Sughrue ME, Rutkowski MJ, Shangari G, Fang S, McDermott MW, Berger MS, Parsa AT. Anatomic location is a risk factor for atypical and malignant meningiomas. **Cancer** 2011;117(6):1272-8.

resident gazette



selected publications

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Michael C. Oh MD, PhD completed his undergraduate studies at Reed College, majoring in Biochemistry and Molecular Biology. His senior thesis project was completed at **Oregon Health & Sciences University** (OHSU), studying the synaptic modulation by mGluRs in the dendrodendritic synapses of the olfactory bulb. He then entered the Medical Scientist Training Program at OHSU to start his medical training as well as graduate studies in the Neuroscience Program at the Vollum Institute. Under the mentorship of Thomas Soderling PhD, he completed his PhD work on the molecular mechanisms of glutamate receptor trafficking to excitatory hippocampal synapses during longterm potentiation. He was awarded several grants for his graduate work, including an F30 NRSA.

Dr. Oh began his neurosurgery training at UCSF in 2008, after completing an internship in general

surgery at UCSF. He worked closely with Andrew Parsa MD, PhD throughout his residency and was awarded an F32 NRSA and a Neurosurgery Research and Education Foundation (NREF) fellowship to support his research in Dr. Parsa's lab. He described the overexpression of calcium-permeable glutamate receptors in glioblastomaderived brain tumor stem cells, which was published in PLoS ONE and recognized with the Preuss Award for best basic science research paper in the tumor section of the 81st AANS annual scientific meeting.

After completing his residency in June 2013, Dr. Oh joined the Moody Brain and Spine Institute at the Methodist Dallas Medical Center, where he is pursuing his interests in skull base tumors and complex spine surgeries.



selected publications

Theodosopoulos PV, Ringer AJ, McPherson CM, Warnick RE, Kuntz C 4th, Zuccarello M, Tew JM Jr. Measuring surgical outcomes in neurosurgery: implementation, analysis, and auditing a prospective series of more than 5000 procedures. J Neurosurg 2012;117(5):947-54.

Theodosopoulos PV, Pensak ML. Contemporary management of acoustic neuromas. Laryngoscope 2011;121(6):1133-7.

Theodosopoulos PV, Leach J, Kerr RG, Zimmer LA, Denny AM, Guthikonda B, Froelich S, Tew JM. Maximizing the extent of turnor resection during transsphenoidal surgery for pituitary macroadenomas: can endoscopy replace intraoperative magnetic resonance imaging? J Neurosurg 2010;112(4):736-43.

Theodosopoulos PV, Guthikonda B, Brescia A, Keller JT, Zimmer LA. Endoscopic approach to the infratemporal fossa: anatomic study. Neurosurgery 2010;66(1):196-203. Philip Theodosopoulos MD is the director of the Skull Base Tumor Program and professor and vice chairman of neurological surgery at UCSF. He recently came to UCSF from the University of Cincinnati, where he served as the residency program director and the director of skull base surgery for the past decade.

Dr. Theodosopoulos completed his undergraduate work at the Massachusetts Institute of Technology and medical school at Stanford University. He completed his neurosurgical training at UCSF and a fellowship in cerebrovascular and skull base surgery at the Brigham and Women's Hospital, Harvard University. His primary clinical interests involve the treatment of skull base lesions. Dr. Theodosopoulos served as the Co-PI for the largest prospective multi-center trial of the surgical treatment of acoustic neuromas and currently serves on the Medical Advisory Board of the

Acoustic Neuroma Association. He has extensive expertise in the endoscopic treatment of pituitary adenomas and chordomas and has pioneered new surgical approaches to the skull base.

As the co-director of the Goodyear Microsurgical Laboratory at the University of Cincinnati he lead a prolific team that developed novel surgical corridors to the skull base, including the first description and clinical application of the endoscopic approach to the infratemporal fossa.

He has been faculty for more than 50 national and international surgical courses and serves on the Congress of Neurological Surgeons Education Committee. Dr. Theodosopoulos also has extensive expertise in the field of outcomes research; he completed the UCSF Outcomes Research and Clinical Epidemiology full curriculum as a resident and has remained involved in outcomes research at the local and national level. Matthew Potts MD was born and raised in Fairfax, Virginia. He attended the Massachusetts Institute of Technology as an undergraduate, majoring in Biology, and then spent a year in Karlsruhe, Germany studying the effects of glucocorticoids on dendritic cell function and maturation.

In 2001 Dr. Potts entered the UCSF School of Medicine where his interest in neurosurgery began after shadowing several UCSF faculty in the clinic and operating room. In 2004 he was awarded a Howard Hughes Medical Institute Medical Research Fellowship to conduct research in the laboratories of Linda Noble-Haeusslein PhD and John Fike PhD, investigating the effects of traumatic brain injury on hippocampal neurogenesis and behavior.

Dr. Potts began his neurosurgical training at UCSF in 2007 and became particularly interested in the treatment of cerebrovascular disease. He has conducted several studies on the treatment of arteriovenous malformations in adults and children and has worked closely with Michael Lawton MD in developing skills in open cerebrovascular surgery. In addition, Dr. Potts was awarded an NIH National Research Service Award to conduct research in the laboratory of Daniel Lim MD, PhD, where his work has helped to characterize the role of a specific neuronal transcription factor in postnatal neurogenesis.

After finishing his training in June 2013, Dr. Potts went on to begin a fellowship in neurointerventional surgery with Howard Riina MD and Peter Kim Nelson MD at the New York University School of Medicine. He then anticipates a career in academic neurosurgery where he hopes to combine his interests in cerebrovascular surgery and the treatment of brain injury.

Phiroz E. Tarapore MD was born in Mountain View, California, and grew up in Lafayette, California. He attended Stanford University as an undergraduate, where he received degrees in Biological Science and Computer Science. He then attended medical school at UCSF, where he subsequently stayed for residency in Neurological Surgery.

During his residency, Dr. Tarapore developed a strong research interest in functional imaging and presurgical mapping with transcranial magnetic stimulation (TMS). In collaboration with Sri Nagarajan PhD, Director of the Biomagnetic Imaging Laboratory, he has developed and validated techniques for mapping cortical regions associated with motor and speech pathways using magnetoencephalography (MEG), and established the first protocols for using navigated TMS for presurgical speech and motor mapping at UCSF. This work was funded by a National Research Service Award. Currently, Dr. Tarapore is developing novel

diagnostic and therapeutic strategies for treating patients with chronic traumatic brain injury.

Dr. Tarapore has recently joined the faculty of the Department of Neurological Surgery at UCSF, where he will continue to pursue his research as the head of the new Core Facility for Navigated TMS. This exciting new project will make TMS-based mapping available to the UCSF community, both inside and outside the Department of Neurological Surgery. It will also be available for collaborative efforts with the Departments of Neurology and Psychiatry. Dr. Tarapore is also an attending neurosurgeon on the clinical services at the San Francisco VA Medical Center and San Francisco General Hospital.

To unwind, Dr. Tarapore loves to play classical piano. He is a new resident of Piedmont, where he lives with his wife, who is a retinal specialist, their 3-year-old daughter, and their baby boy.



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nearaburgery news & notes



Mitchel Berger MD devoted his presidential address to patient safety and quality of care at the annual meeting of the AANS. Image provided by the AANS.

81st Annual Meeting of the American Association of Neurological Surgeons Highlights Quality and Safety for Patients

Chair of Neurological Surgery at UCSF, Mitchel Berger MD, completed his term as president of the AANS and lead the Annual Scientific Meeting in New Orleans from April 20-May 1, 2013. The theme of this year's meeting "Changing Our Culture to Advance Patient Safety," has been an important issue for Dr. Berger throughout his career and was the topic of his presidential address. Following his service to the AANS, Dr. Berger now serves as president elect of the American Academy of Neurological Surgery.

Watch the 2013 AANS Presidential Address on neurosurgical patient safety at: http://bit.ly/16fybr3

At a workshop for caregivers, neuro-oncology nurse practitioner Margaretta Page talks with Jack Glazer, supporter of the UCSF Brain Tumor Center and caregiver to his wife Zelda before she passed away from brain cancer. Mr. Glazer generously provides space for the UCSF Neuro-Caregiver Collaboration to hold meetings in his San Francisco home.

A Workshop for Caregivers of Patients with Brain Disorders

On May 4, 2013 over 100 caregivers attended a free workshop at UCSF's Mission Bay campus focused on coping with the unique challenges of caring for adults with brain disease.

While there are many available support groups for patients, the needs of caregivers are often neglected. The workshop consisted of a series of talks aimed at common issues faced with disorders that affect the brain, such as decline in cognition, behavioral changes, and effects of treatment. There were also presentations on practical issues such as estate planning, talking to children about illness, and plans for advanced care.

Assistance in accessing resources was a main objective of the workshop, but another important outcome was the communication between caregivers. A panel of individuals shared their experiences in order to talk about specific difficulties and about how they arrived at decisions, as well as to give insight to help other caregivers prepare for the future.

"One of the most valuable things that happened was the connections people made," said nurse practitioner Margaretta Page. "I was able to introduce two women who both had young children and were going through a lot of the same issues. It helped them to meet and realize they were not alone in this difficult experience."

The event was organized by the UCSF Neuro-Caregiver Collaboration – a multidisciplinary group of health care providers who span various neurological disease disciplines. The day was supported by the Gordon Murray Caregiver Initiative, Lady Bess Fishback and UCB, Inc. Their generous contributions provided a hot buffet lunch, parking, door prizes, and chair massage for attendees.

Expansion of the UCSF Surgical Movement Disorders Clinic

The multidisciplinary surgical movement disorders clinic was awarded a \$400,000, two-year "Center of Excellence" grant from the Bachman-Strauss Foundation to further develop its clinical infrastructure.

In Memoriam

The Department of Neurological Surgery honors the memory of William Young MD, the James P. Livingston Endowed Chair in the Department of Anesthesia and Perioperative Care, who passed away on August 1, 2013. Dr. Young was a remarkable scientist who founded the UCSF Center for Cerebrovascular Research. He was also a wonderful mentor and an esteemed colleague, and his absence is felt throughout the entire UCSF community.



A phenotype-based screen of 320 FDA-approved compounds revealed that the antihistamine clemizole can inhibit seizures in a zebrafish model of Dravet syndrome.

Potential Drug Discovered for Dravet Syndrome

Scott Baraban PhD and researchers in his laboratory have discovered that the antihistamine clemizole can prevent seizures in a zebrafish model of Dravet syndrome. This rare genetic disorder manifests in early childhood and is characterized by daily seizures, as well as cognitive and social deficits.

Dr. Baraban's zebrafish have a mutation identical to the one that causes Dravet syndrome and were used to screen a library of existing, FDAapproved compounds – including clemizole – to see if any would prove effective against the disease's symptoms. The mechanism by which clemizole blocks seizures is unknown. Ten other antihistamines were screened, but none of them prevented seizures.

Senior staff research associate Matthew T. Dinday BA and postdoctoral fellow Gabriela A. Hortopan PhD were co-authors of this study, published in *Nature Communications*.

Baraban SC, Dinday MT, Hortopan GA. Drug screening in Scn1a zebrafish mutant identifies clemizole as a potential Dravet syndrome treatment. **Nat Commun** 2013;4:2410.

Transplanted Progenitor Cells Cure Epilepsy in Mice

The laboratories of Scott Baraban PhD and Arturo Alvarez-Buylla PhD have published the first report demonstrating that progenitor cells transplanted into the hippocampi of mice with mesial temporal epilepsy can halt or significantly reduce seizures. In their experiments progenitor cells derived from the medial ganglionic eminence region of the brain migrated from the injection site and differentiated into functional inhibitory neurons.

Hunt RF, Girskis KM, Rubenstein JL, Alvarez-Buylla A, Baraban SC. GABA progenitors grafted into the adult epileptic brain control seizures and abnormal behavior. Nat Neurosci 2013;16(6):692-7.

UCSF Walks for Brain Tumors

On May 4, 2013, the Bay Area Brain Tumor Walk raised important funds for the National Brain Tumor Foundation. Staff and supporters from the Department of Neurological Surgery joined the event in Golden Gate Park.



Manish Aghi MD, PhD, associate professor of neurological surgery, has been appointed director of the Congress of Neurological Surgeons' Guidelines Committee Project to produce guidelines for the management of pituitary tumors.

Michael Beattie PhD, professor of neurological surgery, will serve as Principal Investigator of a new translational research award from the Department of Defense on the effects of early, acute care on autonomic outcomes in spinal cord injury. Jacqueline Bresnahan PhD, Adam Ferguson PhD, and Geoffrey Manley MD, PhD of the UCSF Brain and Spinal Injury Center are the project's Co-Investigators.

Aaron Clark MD, resident in the Department of Neurological Surgery, received the 2013 Harold Rosegay Young Investigator Award from the San Francisco Neurological Society.

Dario Englot MD, resident in the Department of Neurological Surgery, received the 2013 John Hanbery Award for Best Clinical Neurosurgery Paper from the San Francisco Neurological Society.

Michel Kliot MD, professor of neurological surgery, has joined the Neurosurgery Editorial Review Board as an Associate Editor in the area of Peripheral Nerve.

Paul Larson MD, associate professor of neurological surgery, was awarded a U01 grant from the NIH to begin a pilot trial of deep brain stimulation in the treatment of refractory tinnitus.

Michael Lawton MD, professor and Tong Po Kan Endowed Chair of Neurological Surgery, was chosen to give the prestigious Hunt-Wilson Lecture at the annual meeting of the American Association of Neurological Surgeons in New Orleans, LA.

Claudia Petritsch PhD, assistant professor of neurological surgery, was awarded a research grant from the foundation Voices Against Brain Cancer for her project "Interrogation of the Glioblastoma Exome to Overcome Therapy Resistance."

The Childhood Brain Tumor Foundation honored Michael Prados MD, professor and Charles B. Wilson Endowed Chair of Neurological Surgery, for his achievements in translational research and care for children with brain tumors at an event in Los Angeles on June 4, 2013.

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selected recent publications from the department of neurological surgery

Abdul-Jabbar A, Berven SH, Hu SS, Chou D, Mummaneni PV, Takemoto S, Ames C, Deviren V, Tay B, Weinstein P, Burch S, Liu C. Surgical site infections in spine surgery: identification of microbiologic and surgical characteristics in 239 cases [published online ahead of print July 18, 2013]. Spine (Phila Pa 1976). doi: 10.1097/BRS.0b013e3182a42a68.

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