TMU
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1960

Nerve Excitability International Symposium

May 2, 2019

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Taipei Municipal Wan fang Hospital (Managed by Taipei Medical University)

臺北神經醫學中心
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TNI

Introduction of Taipei Medical University

Taipei Medical University (TMU), formerly known as Taipei Medical College (TMC), was founded on June 1, 1960 by Dr. Shui-Wang Hu, Dr. Cheng-Tien Hsu and other medical professionals and devoted educators. TMU is located on Wuxing Street in eastern Taipei.

Most of more than 30,000 TMU graduates serve in medical institutions and clinics, while many others are prominent figures in the fields of research, politics, and business. TMU has 9 colleges, 12 undergraduate schools and 14 graduate institutes as well as three affiliated hospitals - TMU Hospital, Wan Fang Hospital, and Shuangho Hospital. With approximately 3,000 beds, TMU is one of the largest health care systems and offers top-quality teaching, research and clinical services in the Taipei metropolitan area. We work continuously to improve the quality of teaching, research and clinical services with the goal of becoming a fully internationalized university that ranks in the top tier worldwide.

Taipei Medical University Hospital

Taipei Medical University Hospital (TMUH) has been serving Taipei for thirty years. Conveniently located near Taiwan's landmark Taipei 101 tower, TMUH offers a warm atmosphere and friendly environment as well as world-tier medical equipment, top-quality medical personnel and patient-centered service. The mission of TMUH encompasses education, research and service through innovation, excellence and commitment to life.

We provide our international friends the same high-quality, efficient and accessible medical services. Our steps toward becoming an internationalized medical center include overseas emergency medical transportation, educational exchanges and medical missions. In addition, we help expatriates in Taiwan with quick and convenient medical services and provide assistance for overseas medical activities, collaborating with the government in expanding medical diplomacy as well as setting up a global network of medical contacts.

Taipei Medical University Wan Fang Hospital

Wan Fang Medical Center dedicated to serving the surrounding area, and is committed to community health promotion. Built in 1989, the Wan-Fang Hospital is the first hospital owned by Taipei City government while run by civilians. In 1998, it passed the Regional Hospital Accreditation and was awarded the international quality certificate of ISO-9002. In 2006, it was awarded the Joint Commission International (JCI) Accreditation. It is the Affiliate Hospital of Taipei Medical University and includes 42 integrated departments of medicine.

Taipei Medical University Shuang Ho Hospital

Shuang Ho Hospital opened on July 1, 2008, with 1580 beds. It is the largest hospital in Taipei County, but also forms a medical “golden triangle” with the Taipei Medical University Hospital and Wan Fang Medical Center, giving a total capacity of over 3000 beds.

Shuang Ho Hospital focuses on providing emergency and critical care, as it is responsible for first response for Taipei County as the only hospital with a medical helicopter and landing pad. Shuang Ho also has the largest dentistry department, with general and family dentistry and six additional specialized clinics. The hospital has the nation's first disabled patient oral health care center to serve the more than 130,000 disabled people in Taipei County. The Kidney Dialysis Center's method of isolating beds, equipment and sections leads the nation in reducing hepatitis C infection. The hospital plans further expansion in the areas of cancer treatment, neurology, minimally invasive surgery, optometry and vision science, health management, cardiology, rehabilitation, trauma surgery and international medical care.

Program at a Glance

May 2nd, 2019 (Thursday)

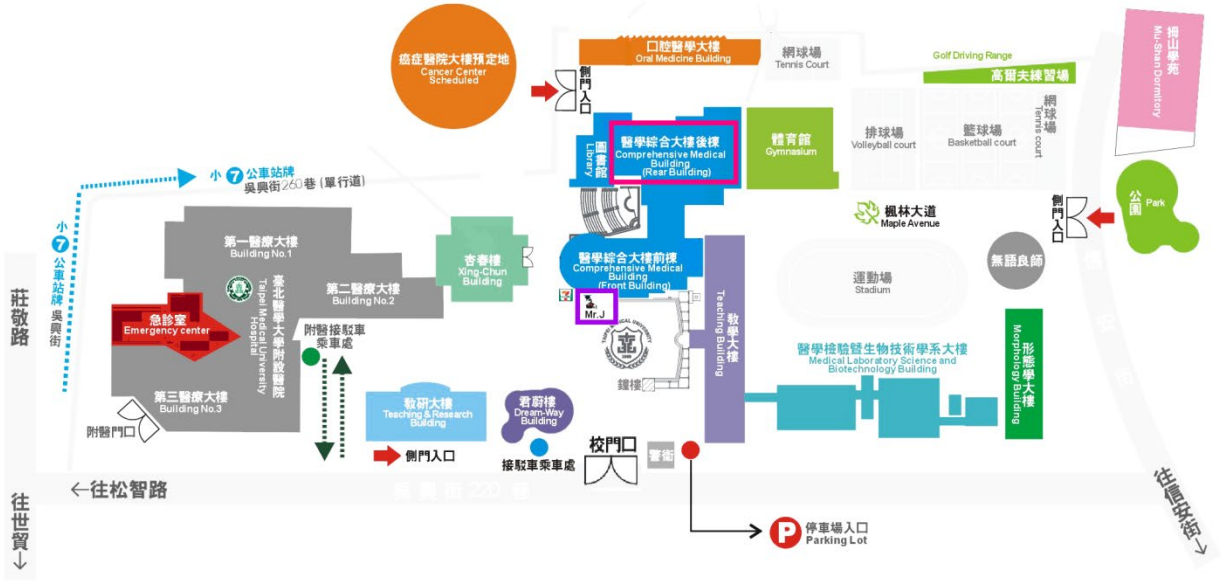
Location: 8F Conference Hall,
United Medical Building (Back Building)

Time	Schedule
08:45~08:55	**Opening Remarks** ***Chair: Sung, Jia-Ying/ Cindy Shin-Yi Lin*** ***President Lin, Chien-Huang*** ***Superintendent, Tu, Yong-Kwang***
08:55~09:00	Group Photography
09:00~09:30	**Clinical Axonal Excitability: It's a tool not a toy for clinical translation** ***Professor Cindy Shin-Yi Lin***
09:30~10:00	**Current concepts of the physiological basis of changes in axonal excitability** ***Professor David Burke***
10:00~10:30	**Coffee Break**
10:30~11:00	**ALS split hand (motor nerve terminal excitability)** ***Professor Satoshi Kuwabara***
11:00~11:30	**Recent treatment strategy in POEMS syndrome and excitability measurements** ***Professor Sonoko Misawa***
11:30~12:00	**Discussion** ***Professor Sung, Jia-Ying/ Professor Cindy Shin-Yi Lin***
12:10-14:00	**Lunch**
14:00~14:30	**Nerve excitability test in SMA patients** ***Dr. Lai, Hsing-Jung***
14:30~15:00	**Modelling the myelinated axon: Insights into mechanisms of human disease** ***Dr. James (Tim) Howells***
15:00~15:30	**Coffee Break**
15:30-16:00	**Elucidating unique axonal dysfunction pattern causing motor deficits in nitrous oxide abuse** ***Dr. Jowy Tani***
16:00- 17:00	**Dicussion & Closing remark** ***Professor Hu, Chaur-Jong/ Professor Sung, Jia-Ying/ Professor Cindy Shin-Yi Lin***
17:00	**Transportation to banquet**
18:30-20:30	**Dinner**

Campus Map

臺北醫學大學
TAIPEI MEDICAL UNIVERSITY

臺北醫學大學校區及附屬醫院平面分佈圖
Campus Map



Opening Remarks

Name: Chien-Huang Lin

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Opening Remarks

Name: Yong-Kwang Tu

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Closing Remarks

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Chair

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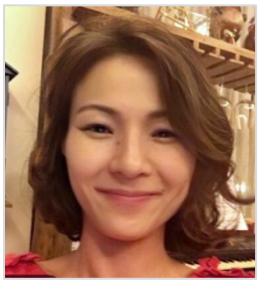
Chair



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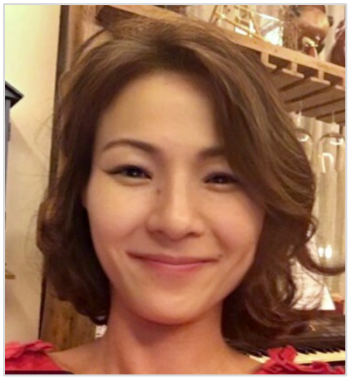
Clinical Axonal Excitability: It's a tool not a toy for clinical translation



Name: Cindy Shin-Yi Lin

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Abstract

Axonal excitability studies have emerged as a recent novel non-invasive threshold tracking technique that offers complementary information to conventional nerve conduction studies. Such novel tools allow for the assessment of peripheral axonal biophysical properties that include ion channels, energy-dependent pumps and membrane potential in health and disease. Over the past 20 years, with advances in technique and development of protocols, in a short period of time, measurement of multiple excitability indices can be achieved that provide insights into different aspects of peripheral nerve function. The assessment of nerve excitability has promoted their application in clinical setting, investigating disease pathophysiology such as in metabolic, toxic and demyelinating neuropathies, amyotrophic lateral sclerosis, stroke, spinal cord injury and inherited channelopathies. Moreover, this technique may have diagnostic and therapeutic implications that may encompass a broader range of neurodegenerative disorders that covers the full age spectrum from children to adulthood, it bring the dynamics of axonal development to the clinical domain and serve to further illuminate pathophysiological mechanisms that occur during development. Taken together, this powerful technique could potentially be incorporated into routine clinical practice to better assess peripheral nerve functions.

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Current concepts of the physiological basis of changes in axonal excitability

Name: David Burke

Current position:

Professor of Neurology at Royal Prince Alfred Hospital and Sydney Medical School, University of Sydney

Abstract

Nerve excitability has been studied in human subjects using threshold tracking for >30 years, during which there have been major advances in our understanding of the mechanisms underlying different measures, in both health and disease. Some processes are not as simple as once thought. No single measure can be interpreted in isolation: coherent changes in a number of measures must be demonstrated before conclusions can be drawn about changes in pump activity or different ion channel currents. No individual ion channel is uniquely responsible for any one process, and most processes can be altered through a number of different mechanisms.

The excitability of an axon normally reflects its membrane potential, but not always. During ischaemia, sodium channels are inactivated by the depolarization and blocked by ischaemic metabolites, so that the true change in membrane potential cannot be measured accurately by the change in threshold. When an axon discharges, the return to the pre-discharge level of excitability involves a sequence of overlapping processes, **refractoriness, superexcitability and late subexcitability**, and no one process determines any one measure. For example, although the major determinant of refractoriness is inactivation of sodium channels, refractoriness can be modulated by ~10% by the activity of slow potassium channels activated when the axon discharges. If the paranodal seal is disturbed, current can access more easily fast potassium channels, which in normal nerve are sequestered under the myelin sheath, and these channels may then alter refractoriness. Superexcitability and late subexcitability are due to two processes that overlap, such that the peak of late subexcitability reflects the balance between excitation due to the depolarizing afterpotential and hyperpolarization due to the gradual closure of slow potassium channels activated by the discharge. The take-away message is that the mechanisms that apply in healthy subjects may not be applicable in diseased nerve.

In the past, we have considered that greater expression of persistent sodium channels was responsible for the longer **strength-duration time constant** of sensory axons than motor axons. There does seem to be a greater persistent sodium current on sensory axons, but this is not due to a greater number of channels: it is probably because sensory axons are depolarized by ~4 mV relative to motor. In **threshold electrotonus** we can make valid measurements only if the conditioning currents are subthreshold. Sensory axons are commonly activated by 40% depolarization, and their discharge produces a "notch" on the electrotonus curve. This is unusual in motor axons unless they are already depolarized. In such instances, weaker depolarizing currents, perhaps 30%, must be used to produce valid responses, and plots with a "notch" must not be used in modelling. With hyperpolarizing currents, inward rectification is not adequately revealed when the current is 40% of threshold for 100 ms. We now recommend stronger and longer currents: -70% for 200 ms and -100% for 300 ms. When we hyperpolarize axons by >60% we deactivate all conductances except two: I_h and the leak conductance. It is likely that HCN1 is expressed on human axons, and largely determines why the lowest threshold motor axons are of low threshold. Whether other HCN isoforms (and heteromers) are expressed on human axons is not known, and probably cannot be revealed using our tests because their time constants are longer. If expressed their activity would probably show up only as a change in membrane potential. The variability of hyperpolarizing threshold electrotonus in different subjects is quite large, but most of this is due to individual differences in I_h. Within any one subject hyperpolarizing threshold electrotonus is quite similar on different occasions. The individual differences are probably not due to differences in the expression of HCN channels on the axons: they are probably due to differences in the gating of a similar number of channels, in particular in the voltage for half-activation of HCN channels. This may well be also true in a number of pathologies where abnormal inward rectification has been described (e.g., stroke, porphyria). The take-away message is that a change in current does not require a change in the number of channels: the same current can be produced by a change in membrane potential or by a change in how those channels are activated.

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Recent treatment strategy in POEMS syndrome and excitability measurements

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Current position:

Associate professor of Department of Neurology, Graduate School of Medicine, Chiba University, Japan

Abstract

POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome is a rare plasma cell disorder which causes progressive demyelinating neuropathy. The pathophysiology of neuropathy in POEMS has not been fully elucidated, but should be associated with multiple upregulated cytokines, such as vascular endotherial growth factor (VEGF).

Axonal excitability measurements and nerve ultrasound in POEMS syndrome showed longer strength-duration time constant, fanning-out of threshold electrotonus curves, greater threshold changes in a hyperpolarizing current-threshold relationship, and nerve enlargement. Serum VEGF levels and the extent of nerve edema partly correlated with nerve conduction slowing, as well as persistent sodium currents and inward rectification. Sequential examinations on nerve excitability and ultrasound were performed before and 3 months after treatment. After therapeutic intervention, levels of serum VEGF were significantly decreased. Nerve cross-sectional area also reduced after treatment, suggesting that edema associated with elevated VEGF is a major cause of nerve enlargement. In excitability testing, superexcitability and threshold change to 100% hyperpolarizing conditioning currents in current-threshold relationship significantly changed towards normal.

Recently, treatments for myeloma have been applied to POEMS syndrome and the prognosis has been much improved. Autologus stem cell transplantation, immune modulatory drugs, and proteasome inhibitor are major treatment options. Combination of excitability recordings, ultrasound, and VEGF assays could provide new insights into the pathophysiology of neuropathy in POEMS syndrome.

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ALS split hand: distal motor axonal excitability

Name: Satoshi Kuwabara

Current position:

Professor of Department of Neurology, Graduate School of Medicine, Chiba University, Japan

Deputy Editor of the Journal of Neurology, Neurosurgery and Psychiatry

Chief Reviewer of Cochrane Database Systematic Review; “Treatment for POEMS syndrome”

Abstract

In amyotrophic lateral sclerosis (ALS), the split hand syndrome has been increasingly recognized; hand muscle wasting preferentially affects the abductor pollicis brevis (APB) and first dorsal interosseous (FDI) muscles, with relative sparing of the abductor digiti minimi (ADM). The physiological mechanisms underlying the split hand in ALS are not sufficiently understood but both cortical and spinal/peripheral mechanisms are probably involved. Short interval intracortical inhibition (SICI), a biomarker of cortical excitability, was significantly reduced more prominently in APB/FDI., supporting a cortical mechanism. But peripheral axonal excitability studies have suggested that APB/FDI motor axons have more prominent persistent sodium currents than ADM axons, leading to higher axonal excitability and thereby more ready degeneration.

Separately, after motor point stimulation, alternation of excitability indices in ALS is much more prominent at the motor point than at the wrist, and this is consistent with evidence that fasciculations mostly arise from the nerve terminals. Frequent use of thenar complex muscles may lead to greater oxidative stress and metabolic demands at both upper and lower motoneurons, and the initial event in ALS may occur at the motor nerve terminals.

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Nerve excitability test in SMA patients

Name: Hsing-Jung Lai

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Abstract

Spinal muscular atrophy (SMA) is an autosomal recessively inherited motor neuron disorder, characterized by progressive muscle weakness, especially in the torso and proximal limbs. Although the mechanism of SMA, namely SMN deficiency, is well known, the underlying pathophysiology, especially regarding electrophysiology, is still not fully understood. We investigated the pathologic changes of nodal and internodal currents with nerve excitability test in SMA patients and a mouse model of SMA. Increased inward rectification in the current-threshold relationship and increased overshoot after hyperpolarizing threshold electrotonus, which indicates increased hyperpolarization-activated cyclic nucleotide-gated (HCN) current, were identified with nerve excitability test in SMA patients, and these findings correlated with disease severity. In a mouse model of mild SMA, increased inward rectification in the current-threshold relationship was reproducible and preceded the decline of compound motor action potential amplitudes. Voltage-clamp recording in dissociated spinal motor neurons from SMA mice showed that increased HCN current was mainly from increased HCN current density, rather than altered biophysical properties of HCN current. Furthermore, quantitative PCR showed increased HCN1 and HCN2 gene expression in the spinal cord tissues of SMA mice, and Western blotting of the spinal cord and sciatic nerves showed increased HCN1 and HCN2 protein expression level. Treatment with ZD7288, an HCN channel blocker, also reduced early mortality, improved motor function, and restored neuromuscular junction architecture without alteration in SMN expression in a mouse model of severe SMA. This study shows that increased HCN current underlies the aberrant excitability of motor axons in SMA and can be a novel non-SMN-target for SMA therapy.

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Modelling the myelinated axon: insights into mechanisms of human disease

Name: James (Tim) Howells

Current position:

Dawn Wallace MND Postdoctoral Fellow – Brain Foundation, The Brain and Mind Centre, Sydney Medical School

Abstract

Mathematical modelling of excitable membranes has a long history dating back to the pioneering work of Hodgkin and Huxley on the giant axon of the squid. A remarkable feat, when you consider that they postulated the presence of ion channels and characterised their function some two decades before their actual identity was confirmed.

The automated measurement of axonal excitability of peripheral nerve using threshold-tracking software (*Qtrac*) has become routine in a number of neurophysiology laboratories around the world. The ease of use and application to many neurological conditions has led to a vast number of studies probing the basis of human disease.

Establishing a difference in an axonal excitability profile is one thing, but determining the most likely mechanisms underlying the change is another. The preference of course is to have data that supports an initial hypothesis, which itself may be based on *a priori* knowledge of the mechanisms of a particular disease or its treatment. Even then, it is useful to have supporting evidence from a mathematical model to strengthen your conclusions. On the other hand, there are circumstances where a mathematical model can be used to tease out mechanisms that are not immediately obvious, but this takes a great deal of care and patience!

Mathematical modelling of axonal excitability has provided useful insight into the underlying mechanisms of human disease, changes due to pharmacological intervention and the differences between animal and human excitability.

The axonal excitability software, *Qtrac* incorporates a model fitting program, MEMFITS, which implements the 'Bostock' model of a human motor axon and has been adapted to sensory myelinated axons. The same model has also been used to model the excitability of motor and sensory axons in the mouse tail. This model is morphologically simple, and it simplifies the task of understanding axonal excitability, as recorded by threshold-tracking studies, by modelling the determinants of the excitability of *a single node of a single axon* and its interaction with an adjacent internode.

It is important to note that this is a mathematical model of healthy nerve, and there are limitations to its ability to model changes in disease, particularly when the disease process involves structural alteration or expression of isoforms not normally present in healthy axons.

In this talk I'll present my approach to modelling through a number of worked examples, and will discuss some of the assumptions, challenges and pitfalls.

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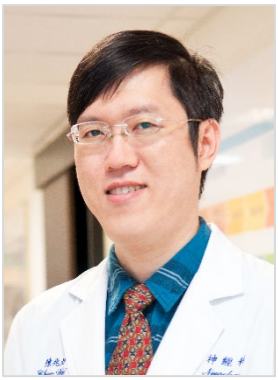
Elucidating unique axonal dysfunction pattern causing motor deficits in nitrous oxide abuse



Name: Jowy Tani

Current position:

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Abstract

Abuse of nitrous oxide (N2O) has an unusually high lifetime prevalence in developed countries and represents a serious concern worldwide. Myeloneuropathy following the inhalant abuse is commonly attributed to the disturbance of vitamin B12 metabolism, with severe motor deficits are often noted. The present study aims to elucidate its underlying pathophysiology.

Eighteen patients with N2O abuse or vitamin B12 deficiency were recruited. Comprehensive central and peripheral neuro-diagnostic tests were performed, including whole spine MRI, and thermal quantitative sensory testing (QST). Specifically, paired motor and sensory nerve excitability tests were performed in order to obtain a complete picture of the sensorimotor axonal damage.

The mean duration of N2O exposure for the N2O abuse patients was 17.13±7.23 months. MRI revealed T2 hyperintensity in 87.5% of the N2O abuse patients and 50% of the vitamin B12 deficiency patients. In N2O abuse patients, the motor nerve excitability test showed decreased in peak response (7.08±0.87 μV, P=0.05), increased latency (7.09±0.28 ms, P<0.01), increased superexcitability (-32.95±1.74%, P<0.05), and decreased accommodation to depolarizing current (TEd(40-60ms) 56.53±0.70%, P<0.05); the sensory test showed only decreased peak response (30.54±5.98 μV, P<0.05). Meanwhile, motor test in vitamin B12 deficiency patients showed only decreased accommodation to depolarizing current (TEd(40-60ms) 55.72±1.60%, P<0.01); the sensory test showed decreased peak response (25.86±3.44 μV, P<0.05) increased superexcitability (-28.58±3.71%, P<0.001), increased subexcitability (8.31±1.64%, P<0.05), and decreased accommodation to depolarizing current (TEd(peak) 67.31±3.35%, P<0.001).

Compared to vitamin B12 deficiency, N2O abuse patients showed prominent motor superexcitability changes and less prominent sensory superexcitability changes, hinting a unique pathological process different from that of vitamin B12 deficiency. N2O abuse might cause axonal dysfunction not only by blocking methionine metabolism but also by toxicity affecting the paranodal region.

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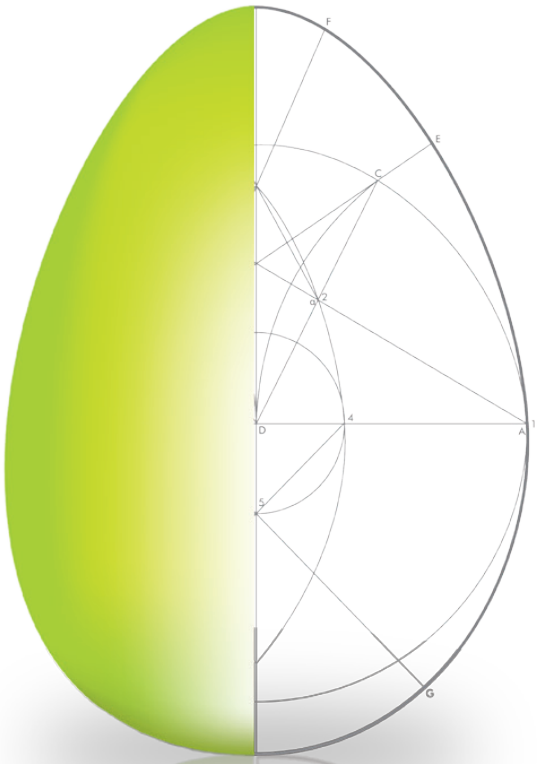

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