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The contents of *EJBM* encompass the results of basic and clinical investigation, as well as those disciplines at the interface of medicine and the social sciences, medico-legal and ethical studies, epidemiology, public policy, and the history of medicine. *EJBM* publishes articles in all fields of biology and medicine, and invites contributions from any scientific or clinical department.

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EJBM COVER ART

On the cover: The processes governing inter- and intra- neuronal communication are highly regulated. Several articles in this issue describe pathologies that result from homeostatic disruption including thiamine deficiency (Nariai et al. pp. 23–24), hyperglycemia (Shabbir and Jadeja, pp. 25–26), and dysregulation of autophagy (Schneider et al. pp. 34–39). The cover image shows an artist's visualization of varied neuronal populations communicating under homeostatic conditions.

Cover artwork by Ruth A. Howe.

SUBMISSIONS

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Origins and Applications of CRISPR-Mediated Genome Editing

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DISCOVERY AND DEVELOPMENT OF CRISPR AND CAS9 (FIGURE 1)

In the late 1980s, a group of researchers interested in the alkaline phosphatase of *Escherichia coli* discovered something odd. In their paper, the authors briefly described a strange genomic topology consisting of a series of 32 nucleotides of unique sequence, flanked by short invariable palindromic repeats on the 3' end of the phosphatase gene that they had been studying (Ishino et al., 1987). The odd genomic architecture they observed is the first known description of a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) array. It would be another 15 years until additional work was done on these novel loci. Further work would reveal that numerous protein-coding genes cluster near CRISPR arrays and that these genes are highly conserved among bacteria and archaea (Jansen et al., 2002). In 2005, a trio of papers began to uncover the function of these pervasive and unusual loci. Bolotin et al., Mojica et al., and Pourcel et al. demonstrated that the unique spacer regions found in CRISPR arrays actually mapped to phage genomes, hinting at CRISPR as a possible adaptive immune response to phage infection through an RNA-guided process (Bolotin et al., 2005; Mojica et al., 2005; Pourcel et al., 2005). The molecular mechanism of this immune response was elucidated in 2012; two papers demonstrated that CRISPR arrays are transcribed into RNA, which is then cleaved and loaded into CRISPR-associated (cas) proteins (cas9, in this case). This RNA:protein complex is sufficient for RNA-guided dsDNA endonuclease activity (Gasiunas et al., 2012; Jinek et al., 2012). Furthermore, Jinek et al. demonstrated that cas9 could be reprogrammed to target novel sequences with an *in vitro* transcribed single guide RNA (sgRNA) (Jinek et al., 2012). This group also demonstrated that two amino acid changes to cas9 could render its nuclease domains non-functional (Jinek et al., 2012), a concept that has been seized upon by other groups to develop novel tools to regulate gene expression.

For many years, researchers had been searching for a tool to induce mutations easily in a targeted fashion. While some headway had been made with Zinc Finger Nucleases, Meganucleases, and Transcription Activator-Like Effector Nucleases (TALENs), all of these techniques had several limitations. Each was either labor intensive, expensive, or both, as the targeting mechanisms were all based on protein-nucleic acid interactions, thereby requiring a custom-designed protein for each gene locus of interest. The promise of RNA-guided nuclease activity afforded by CRISPR-based approaches led numerous groups to recognize immediately

this technology's potential to induce targeted, double-stranded breaks (DSB) in eukaryotes, which previously could only be accomplished with much difficulty. DSBs produced by previously available technologies, and now CRISPR-based systems, are repaired by low-fidelity DNA repair pathways, leading to the production of insertion/deletion mutations (indels)—a class of mutations characterized by the random insertion or deletion of nucleotides at the site of the DSB. The introduction of indels into the coding region of a gene can then, either *de novo* or due to a frame shift, introduce a premature stop codon leading to a truncated protein product, or the induction of non-sense mediated decay of the mRNA transcript itself upon expression of the targeted gene. The production of DSBs can also be used to promote the successful knock-in of novel genetic elements by flanking the novel element with homologous sequences derived from the targeted locus, and co-delivering the flanked novel element along with the sgRNA and cas9.

The first demonstration of RNA-guided mutation in eukaryotic cells occurred in 2013 (Cong et al., 2013; Mali et al., 2013). While reprogramming sgRNAs was not a novel discovery at this point—Jennifer Doudna's group had already shown that cas9 could easily be reprogrammed to cleave DNA *in vitro*—these papers were instrumental in providing the scientific community with a well-documented set of tools that could easily be implemented by other labs. Weeks after these papers were published, any lab could obtain CRISPR constructs, purchase a pair of oligonucleotides, perform a simple cloning reaction, and quickly create knock-out or knock-in cell lines (Cong et al., 2013; Mali et al., 2013) or with some additional equipment, animals (Wang et al., 2013). With this single tool, both of these activities have now become technically and financially accessible to a variety of labs, and are no longer confined to the sole domain of industry labs or particularly well-funded academic labs.

However, cutting DNA is by no means the only application for CRISPR. The nuclease-dead cas9 that Doudna's group produced in 2012 was shown to be still capable of binding the targeted locus and disrupting either transcriptional initiation or elongation via steric hindrance, thereby repressing gene expression without inducing DSBs in the genome (Qi et al., 2013). Other groups have further exploited this characteristic by creating cas9 fusion proteins, allowing for fine-tuned adjustment of gene expression (Gilbert et al., 2013), assessing epigenetic state (Hilton et al., 2015; Kearns et al., 2015), and even fluorescent imaging of the genome in live cells (Chen et al., 2013). Furthermore, by taking advantage

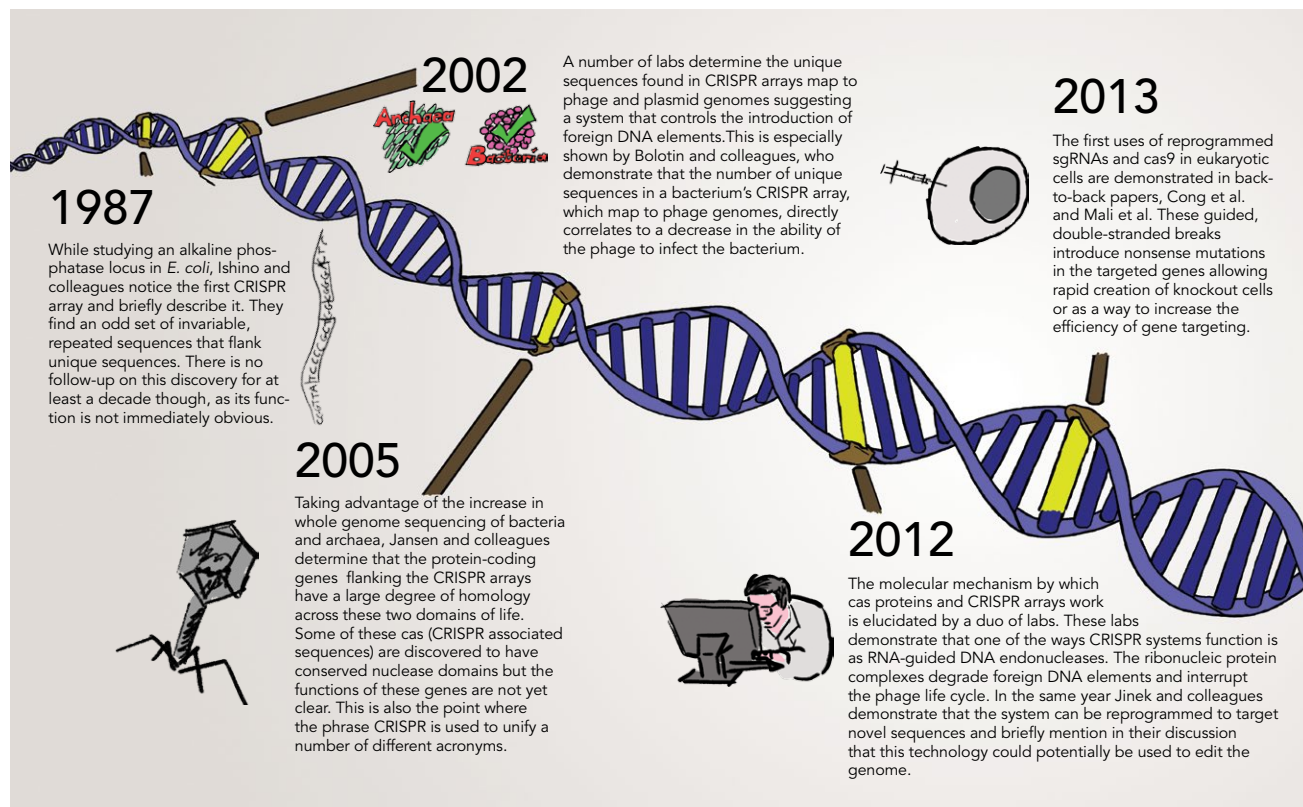


Figure 1 | The Discovery and Development of CRISPR and Cas9

of the modular nature of sgRNAs and the ever-decreasing price of oligonucleotide synthesis, multiple screening libraries (Doench et al., 2016; Joung et al., 2016; Konermann et al., 2015; Sanjana et al., 2014; Shalem et al., 2014; Wang et al., 2014) have been produced to knock out genes by the introduction of indels into the coding sequence, as well as to regulate their expression by targeting the proximal promoters of genes and using some of the fusion proteins described above.

With all these possible uses, CRISPR-based technologies have captured the imagination of biologists, and rightly so. However, with new techniques comes the potential for novel sources of error. Therefore scientists using these systems should consider the following: How specific is the sgRNA in question? Do multiple sgRNAs targeted to the same gene locus recapitulate similar phenotypes? Is cas9 transiently or constitutively expressed? As a control, is cas9 protein used alone or in combination with a non-targeting sgRNA? To paraphrase Voltaire, the perfect experiment is the enemy of the appropriately controlled one. Finally, it is imperative to read and understand the technical details of this powerful technology before implementing it in one's own projects. In order to comprehend fully what other research groups are doing, or when a certain flavor of the technology might be useful for one's own studies, it is essential to develop a familiarity with the capabilities and limitations of CRISPR.

MECHANISMS OF CAS9:SGRNA TARGET BINDING AND DNA REPAIR (FIGURE 2)

In the nucleus, the cas9:sgRNA complex rapidly begins to sample (near the speed of diffusion) the genome for any bases that match its protospacer-adjacent motif (PAM) (Jinek et al., 2014; Knight et al., 2015). Upon recognition of the PAM by cas9 the complex slows down, briefly allowing sgRNA to bind the bases 5' of the PAM. If there is little or no base pairing to the genomic DNA, the complex detaches and samples additional PAMs elsewhere. However, if the sgRNA perfectly matches or nearly perfectly matches the genomic sequence, the sgRNA and its genomic complement enter a central channel of the cas9 protein where the complementary genomic DNA is cleaved by one of the two nuclease domains found in the cas9 protein (Anders et al., 2014; Jinek et al., 2014). Simultaneously, the anti-complementary genomic DNA is fed into a second channel of the of cas9 protein where it is also cleaved (Anders et al., 2014). After cleavage, the cas9:sgRNA complex disassociates from the genomic DNA and continues to sample for additional PAMs (Knight et al., 2015). The presence of a double-stranded break within a cell leads to the activation of DNA damage responses, wherein the cell will either repair the break via template-driven homologous recombination (HR), or by non-homologous end joining (NHEJ), a template-independent repair mechanism. The former method will result in an error-free repair, and if an exogenous template is introduced, this repair method will incorporate novel

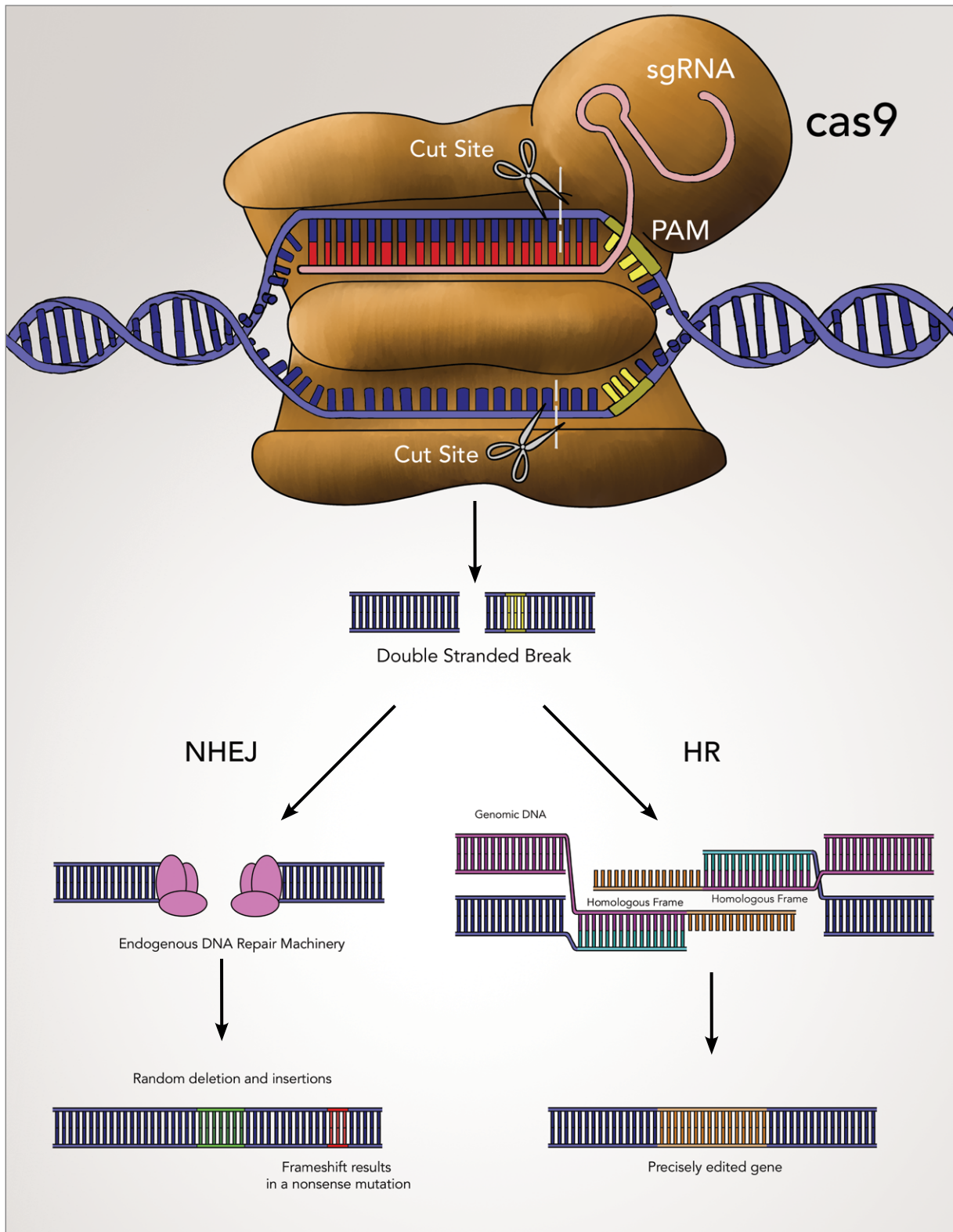


Figure 2 | Mechanisms of cas9:sgRNA Target Binding and DNA Repair

genetic elements into the genome. However, NHEJ will result in the random subtraction or addition of nucleotides at the break site in order to create conditions conducive to sealing the break, but this generally results in a frameshift and a downstream nonsense mutation in the targeted gene.

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Axillobifemoral Bypass: A Brief Surgical and Historical Review

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Peripheral artery disease (PAD) occurs when plaque accumulates in the arterial system and obstructs blood flow. Narrowing of the abdominal aorta and the common iliac arteries due to atherosclerotic plaques restricts blood supply to the lower limbs. Clinically, the lower limb symptoms of PAD are intermittent claudication, discoloration of the toes, and skin ulcers, all due to arterial insufficiency.

Surgical revascularization is the primary mode of treatment for patients with severe limb ischemia. The objective of the surgical procedure is to bypass a blockage in an occluded major vessel by constructing an alternate route for blood flow using an artificial graft. This article presents information on aortoiliac reconstruction, with an emphasis on axillobifemoral bypass grafting.

PERIPHERAL ARTERY DISEASE

Peripheral artery disease (PAD) is defined as a narrowing of arteries that are neither cardiac nor intracranial. It is a growing public health concern affecting 8.5 million people in the United States and 200 million people worldwide (Kullo and Rooke, 2016). The major mechanism of PAD is atherosclerosis, a disease in which plaque accumulates inside the arterial intima. Plaque accumulation obstructs the lumen of the vessel causing a reduction in blood flow, which leads to diminished oxygen supply to the recipient tissues. Certain natural branch points and curvatures within the vascular tree are more susceptible to atherosclerosis due to turbulent blood flow and shear stress. Current understanding suggests that turbulent blood flow at very low shear stress compromises the integrity of the endothelial lining. Such hemodynamic changes appear to be linked to the development of focal atherosclerosis (Davies et al., 1986). Areas known to be frequently affected include the aorta, as well as the coronary and carotid arteries (VanderLaan et al., 2003). Other causes of PAD include inflammatory vasculitis and non-inflammatory arteriopathies (Kullo and Rooke, 2016). The main risk factors for developing PAD are diabetes mellitus and smoking (Kullo and Rooke, 2016). The incidence of PAD increases with age; 20% of people over 60 years old have some degree of PAD (National Clinical Guideline Centre, 2012).

Symptomatic presentation of PAD ranges from leg discomfort and pain at rest, to intermittent claudication, to critical limb ischemia resulting in gangrene and subsequent amputation (Kullo and Rooke, 2016). Other signs of PAD include differences in color and/or temperature of the lower limbs compared with other body parts, as well as pallor on elevation of the lower limb above 60° (Swartz, M. H. 2006).

Diagnosis of PAD typically occurs after symptoms are reported and a thorough physical examination has been

performed. Diagnostic tests include the ankle-brachial index (ABI) test, Doppler ultrasound, the treadmill test, magnetic resonance angiogram, and arteriogram (National Heart, Lung, and Blood Institute, 2015). Upon diagnosis, PAD can be categorized using a number of classification systems. One of the most common, and the most relevant to lower limb ischemia, is the Rutherford classification system (Hardman et al., 2014). This scheme, developed in 1986, distinguishes between PAD-related chronic and acute limb ischemia. The chronic classification system relies on a combination of objective criteria (e.g. ABI) and symptomatic description in determining the classification of PAD. Symptomatic descriptions range from asymptomatic, to increased claudication, to tissue loss (Hardman et al., 2014).

The ABI is the relationship between systolic blood pressure in the ankle and systolic blood pressure in the arm. The normal range is 1.00–1.30. An ABI under 0.90 is indicative of PAD (Kullo and Rooke, 2016). A low ABI suggests that the systolic blood pressure is lower in the legs than in the arms, which indicates possible arterial blockage. The ABI, ultrasound imaging, and treadmill tests are all non-invasive methods of diagnosis.

The objectives of PAD management are to alleviate symptoms, to reduce the risk of adverse cardiovascular events, and to preserve limb function. Smoking cessation, dietary modifications, and other healthy lifestyle changes can improve patient outcomes. Surgical revascularization is required when behavioral modifications are not effective. Often, the initial treatment approach is balloon angioplasty with or without stenting to widen the arterial lumen and improve blood flow (Slovut and Lipsitz, 2012). When an endovascular approach is not feasible, open surgical intervention is necessary to restore adequate blood flow to the lower limbs. The three main open surgical procedures are aortofemoral bypass grafting (AOFBG), axillofemoral bypass

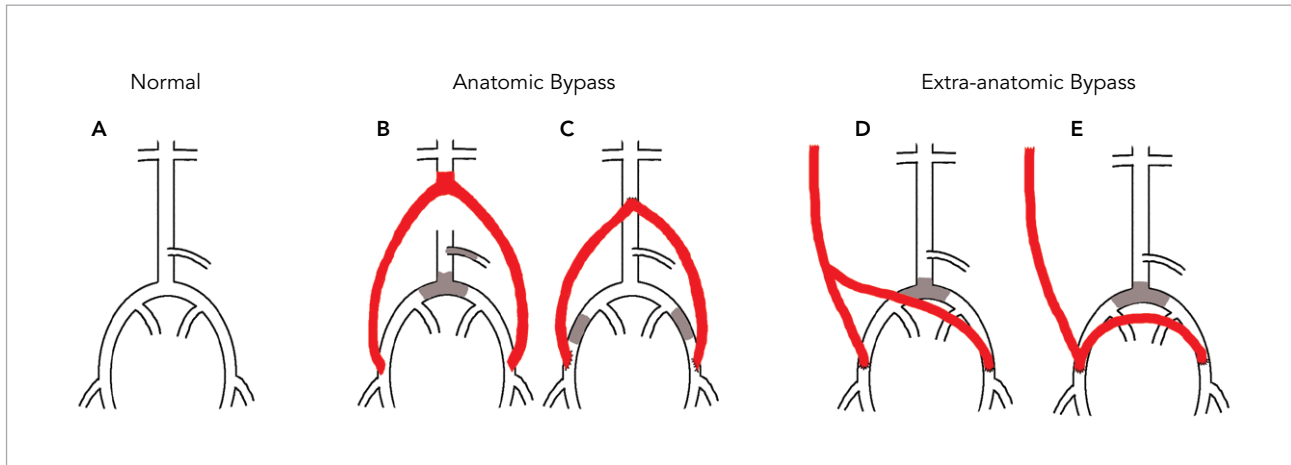


Figure 1 | Aortoiliac reconstruction bypass configurations. A. Normal arterial configuration. B. Aortoiliac graft for inferior mesenteric and common iliac blockage. C. Aortoiliac graft for external iliac blockage. D. Axillobifemoral graft (early version). E. Axillobifemoral graft (current version).

grafting (AXFBG), and aortoiliac endarterectomy (Slovut and Lipsitz, 2012). AOFBG is classified as an anatomic procedure, meaning that the graft is constructed alongside the diseased artery using a transabdominal or retroperitoneal approach. AXFBG is classified as extra-anatomic because the graft is placed subcutaneously and, therefore, does not have spatial relation to the diseased artery throughout most of its length (Slovut and Lipsitz, 2012). Graft configuration is determined based on the location of the occlusion and surgical risk of the individual patient. Figure 1 demonstrates several bypass configurations. The present article focuses on the history and surgical techniques of the AXFBG bypass and refers to Matakas et al. (2016), a reflection presented in this issue on the discovery of an AXbiFBG upon cadaveric dissection.

HISTORICAL CONTEXT AND SURGICAL TECHNIQUE OF AXILLOFEMORAL BYPASS

Prior to the development of the AXFBG, other arterial graft procedures were used to restore adequate blood flow around an area of obstruction. For example, in 1953, Freeman and Leeds published an article describing how the splenic artery was used to bypass the abdominal aorta. In 1960, cross-over grafts were described between the common iliac arteries (McCaughan and Kahn, 1960), and in 1961, thoracic aorta to femoral artery bypass grafts were described (Blaisdell et al., 1961). These procedures were successful in patients with unilateral occlusion; however, they were of limited use for patients with high surgical risk, or those with bilateral occlusion. In 1963, Blaisdell and Hall reported that they successfully performed the first AXFBG. In fact, they performed the procedure on three patients who presented with high surgical risk and bilateral occlusive disease. In one of the patients, AXFBG was performed using only local anesthesia, highlighting the utility of AXFBG in patients who could not tolerate general anesthesia. Further, AXFBG provided a major advantage over other procedures by avoiding abdominal incision and cross-clamping of the

aorta, both of which entail significant physiologic stress to the patient (Blaisdell and Hall, 1963; Al Wahbi, 2010).

In 1966, Sauvage and Wood adapted the AXFBG procedure to accommodate bilateral occlusions and performed the first axillobifemoral bypass graft (AXbiFBG). In the original configuration of these grafts, the bifurcation was placed at the level of the umbilicus (Figure 1D). The flow rates differed to the ipsilateral and contralateral limbs, which affected the patency of these early grafts (Ray et al., 1979). Subsequently, the configuration was changed so that the bifurcation occurred at the femoral hood of the graft (Ray et al., 1979), and this configuration continues to be used today.

Early AXbiFBG grafts were made of crimped, non-supported Dacron®, but problems arose with thromboses due to compression of the graft during sleep (Kenney et al., 1982). Kenney later demonstrated that the use of non-crimped grafts with external support improved the graft's four-year patency rate because they were incompressible (Kenney et al., 1982). Burrell et al. (1982) compared the effectiveness of Dacron® versus polytetrafluoroethylene (PTFE) on graft patency, and found no significant difference in patency rates. These conclusions were replicated and confirmed by Donaldson et al., in 1986.

Other attempts to prevent clot formation in grafts included bonding various agents to the internal surface of the graft material. Some of the agents used were gelatin, collagen, and heparin (Roll et al., 2008; Takagi et al., 2010). It is unclear whether these enhanced grafts had any effect on overall patency rates, as there is limited literature available comparing the functionality of different bonding agents.

The AXbiFBG procedure has been described in the literature several times with slight variations related to the surgeon's preference (Blaisdell and Hall, 1963; Sauvage and Wood, 1966; Mannick and Nabseth, 1968; Al-Wahbi, 2010;

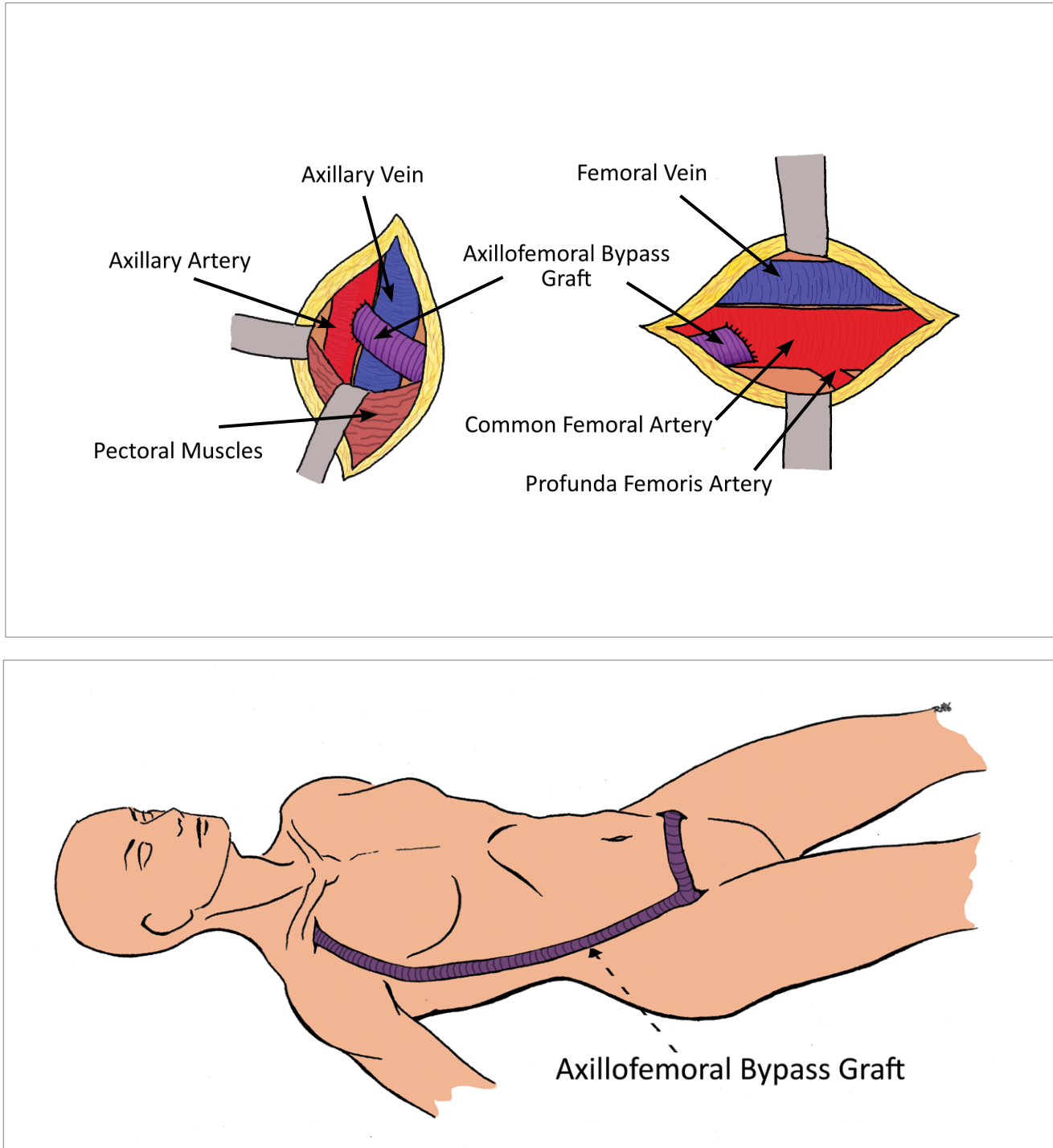


Figure 2 | Axillobifemoral bypass (AXbiFBG) procedure. Illustrated is the axillary anastomosis (top left), femoral anastomosis (top right), and general configuration (bottom). (After Mannick, J. A., and Nabseth D. C. (1968)).

Slovut and Lipsitz, 2012; Jun and Lopez, 2015). The procedure is typically performed with the patient under general anesthesia, but can be performed with local anesthetic, with or without sedation, according to the needs of the patient (Al-Wahbi, 2010).

A schematic for placing the AXbiFBG is depicted in Figure 2. Proximally, a horizontal incision is made just below the clavicle and a small portion (2.5–5 cm) of the proximal axillary artery is freed from the surrounding tissues. The pectoralis major and/or minor muscles are split to facilitate this dissection. Distally, just below the ipsilateral inguinal ligament, a vertical incision is made and the femoral sheath is entered. The common femoral artery is freed and inspected, along with the superficial and profunda femoral arteries. These arteries are evaluated for disease and local endarterectomy is performed if necessary. If placement of a bifemoral shunt is required, the same inguinal technique is repeated on the contralateral side to access and assess that femoral artery (Sauvage and Wood, 1966).

With the proximal (axillary) and distal (femoral) arteries exposed, a subcutaneous tunnel is made along the midaxillary line, connecting the two arteries. When a bifemoral graft is needed, a horizontal tunnel is prepared connecting the two common femoral arteries. The graft is carefully passed through the tunnel and longitudinal arteriotomies are performed to anastomose the graft and the artery (Blaisdell and Hall, 1963). While premade AXbiFBGs are now available, the bifemoral portion can also be anastomosed to an AXFBG (Jun and Lopez, 2015).

Pre-operative considerations for AXFBG include assessment of the axillary arteries to ensure there is no stenosis or other disease. Resting ankle-brachial pressure indices are taken and the patient's surgical risk is assessed. Those patients who have high surgical risk due to prior abdominal surgeries, age, or other health conditions that would preclude them from an anatomic bypass (AOFBG), are frequently able to withstand AXFBG.

Complications of AXFBG include graft thrombosis or infection (Passman et al., 1996; Ray et al., 1979; Burrell et al., 1982; Donaldson et al., 1986), seroma (Donaldson et al., 1986), plexus lesions (Kempczinski and Penn, 1978), and arterial steal syndrome (Kempczinski and Penn, 1978). Patients may need to undergo a thrombectomy or total graft replacement in order to maintain patency. Complications are most likely to occur within the first 36 months following surgery, with the average being 21.5 months (Donaldson et al., 1986). In some cases, if the graft cannot be fixed, patients will undergo amputation (Donaldson et al., 1986). Due to the possibility of developing these severe complications, some have called into question the usefulness of AXFBG (Donaldson et al., 1986). Despite the complication rate, the five-year primary graft patency rate has been reported in the range of 54% (Martin and Katz, 2000) to 80.4% (Passman et al., 1996; Ray et al., 1979). In patients that undergo thrombectomy, as many as 97% can expect no further complications over the following five-year period (Burrell et al., 1982).

Post-operative care for AXFBG patients may include the use of anti-thrombotic agents, particularly in patients who require multiple reoperations to maintain graft patency (Donaldson et al., 1986). Some evidence has shown that anti-platelet medications such as aspirin can be beneficial for patients with synthetic grafts (Slovut and Lipsitz, 2012; Dorffler-Melly et al., 2003). The use of warfarin, however, has been associated with an increased risk of hemorrhage (Slovut and Lipsitz, 2012). Patients should be routinely monitored for recurrence of symptoms, which indicates the development of thrombosis (Slovut and Lipsitz, 2012).

SUMMARY

PAD can be managed using multiple modalities. However, in people with severe disease, surgical bypass grafts are the standard of care. This report discusses the history and surgical techniques of the extra-anatomic procedures known as AXFBG and AXbiFBG. Both the literature and the evidence from the case report (Matakas et al., 2016) support the utility of axillobifemoral bypass graft in restoring adequate blood flow to the lower limbs. The first-year medical students who discovered an AXbiFBG in their anatomy cadaver were so curious about the graft, and the disease that it was used to treat, that they were inspired to learn more and, ultimately, to share what they learned with others.

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Stemming the Medical Brain Drain: A Personal Perspective on a Global Problem

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The term “medical brain drain” refers to the international migration of physicians from the developing world to developed countries. This loss of health professionals contributes significantly to global health inequities. The issue has been framed in terms of ethical, financial, and infrastructural issues, and many attempts have been made to pose solutions that address the respective arms of this multifaceted phenomenon. This article seeks to

explore the medical brain drain from a migrant physician’s personal perspective, contextualized with data and analysis from relevant literature. I conclude that adopting the mindset of “brain circulation” rather than “brain drain” will be a component in paving the way for multidisciplinary solutions to the problems that promote the migration of physicians from resource-limited settings.

The world is set to face a shortage of 4.3 million health professionals required for delivering essential health services (WHO, 2006). Most of these shortfalls occur in the developing world, which, curiously, supplies roughly a quarter of the physicians currently practicing in the United States (Taylor et al., 2011). The term “medical brain drain” refers to this international transfer of resources in the form of human capital, particularly the migration of highly educated individuals from developing to developed countries (Beine et al., 2008). The factors fueling the emigration of physicians and other health workers include elements intrinsic to the exporting country, such as low remuneration and poor working conditions, as well as external influences, such as recruitment by the recipient countries. In combination, these forces significantly drive global health inequities. Taking the example of Pakistan, a country with sizable healthcare disparities, nearly two-thirds of medical students expressed a wish to emigrate, citing factors such as political instability, harassment of doctors in Pakistan, and improved quality of life and training abroad (Sheikh et al., 2012). Although such concrete issues are often blamed when examining the issue of brain drain, conceptualizing the problem on an individual level is an important step in addressing it. For example, Hannah Bradby notes that

nurses and doctors embody the importance of health as a social good such that their emigration from a place with health problems is highly charged.... Attempts to reduce migration out of countries with significant unmet need for healthcare betray a view of healthcare workers as a mobile and transferable resource whose flow is open to regulation. This view potentially ignores workers’ own assessment of their interests, not to mention violations of individual freedom of movement (Bradby, 2014).

The medical brain drain is now firmly on the public health agenda, prompting the debate on how to combat it. Bradby asserts that the view of healthcare workers as commodities is shortsighted, overlooking the agency of migrant physi-

cians as individuals. Perhaps we must re-examine this crisis, and instead leverage the very migration of these individuals to uplift the health systems of their native countries.

My own parents, raised and educated in Bangladesh, left their native country in their late twenties. Both trained physicians, they practiced in government hospitals that served many low-income patients. When I asked my mother where she had eventually seen herself while still a medical student in Bangladesh, she replied that she had imagined teaching in an academic institution in the capital, Dhaka. “I wanted to teach medical students at my alma mater, actually. But there were no career opportunities that weren’t managed by the government; at that time, there were no private hospitals. If you graduated with a medical degree, you had to work at the posting to which you were assigned.”

My mother’s posting was in a rural health center, 60 kilometers (37 miles) outside of Dhaka. Bangladesh’s healthcare system has a tiered structure: Primary care is provided at the *upazila* (sub-district) level, secondary care at the district level, and specialized care at the divisional (city) level. At the upazila level, health complexes are the first-line referral center for primary care, and bring essential health services to the doorsteps of the rural poor (Rahman et al., 2005). Though many countries rely on a similar system to staff rural areas in need of healthcare, the internal maldistribution of healthcare workers is often problematic. In Ghana, for example, although 60% of medical students surveyed responded that they would consider practicing rurally, historically, many doctors have failed to report to rural sites, or left the site soon after reporting (Kotha et al., 2012; Dovlo & Neonator, 1999). In Bangladesh, my mother’s posting was in primary care at an upazila facility, though she had originally planned to specialize. She requested a transfer to a post in Dhaka, which was granted, but before she could begin her posting, my parents married and moved to Hiroshima, Japan, to pursue graduate degrees.

“When you left for Japan, did you plan on returning to

Dhaka?" I asked. My mother explained that if she and my father moved back to Bangladesh, they would not have jobs; the political system at the time discouraged returning to the country upon leaving it. When my mother left, she effectively resigned her post permanently, because she would not be offered another position in a government-run hospital. Notably, the government-subsidized hospitals in Bangladesh are the only institutions that treat primarily low-income patients. Unfortunately, there are only 660 public, government-run hospitals in the country to serve the more than 50 million Bangladeshis living below the poverty line. And though Bangladesh boasts the third-highest rate of underweight children in the world, and is among the top 50 nations with the highest maternal mortality, only 96 maternal and child welfare centers exist in the whole of the densely populated country (Rahman et al., 2005; CIA, 2012).

Although private health facilities have now been established in Bangladesh, privatized care is accessible only to those who can afford it. Many doctors from public hospitals "moonlight" at private centers, part-time. Patients at these facilities often believe that they receive a superior standard of care compared to public hospitals—a disputable assumption, as private hospitals are often attended by the same physicians that serve in public ones. In addition, private clinics are often unaccountable to government standards of service rates and health risks. Though there is little formal data on the differences in private versus public care, one example occurs in rural Bangladesh, where traditional faith healers, homeopaths, untrained pharmacists and allopaths fill the gap in need-based healthcare delivery systems for the rural poor (Rahman et al., 2011). Similarly, among the urban poor, unregulated selling of over-the-counter pharmaceuticals and care-seeking from informal and low-quality unlicensed private clinics exacerbate the already poor health of slum-dwellers (Afsana & Wahid, 2013). Although the recent increase in the establishment of private hospitals in Bangladesh has dissuaded many wealthy patients from seeking care abroad, it has done nothing to deliver essential health services to the poor (Rahman et al., 2005). A similar phenomenon has been observed in India, as well. A survey of Indian doctors in the United Kingdom found that, although a significant number of them intended to return to India, most planned to work in the private sector upon their return—thus leaving the impoverished rural areas without service (Kangasniemi et al., 2007).

Today, my parents are practicing physicians in New York, where 40% of the healthcare workforce is constituted by foreign medical graduates (AMA, 2010). From the moment they left Bangladesh, my parents knew that they would not return to live there. During my mother's five years in Japan, she simultaneously worked toward her PhD and prepared for the U.S. Medical Licensing Examination. She had planned to move to either the U.S. or the U.K. to acquire better training, and says she would have made the same decisions even if she had understood the obstacles foreign medical graduates must overcome to enter the medical profession in the U.S. "The education here is better," she said. "In Bangladesh, there was no opportunity to pursue

a PhD, and training wasn't comparable to [the U.S.]. But at some point in my life, I want to return to Bangladesh to train people."

This was the first I'd heard of my mom wanting to work in Dhaka someday. She had some interesting insights when I probed her on the issue. For one thing, she has never questioned the ethics of developed countries recruiting physicians from less wealthy nations, although this has been an ongoing target of policy change in addressing the medical brain drain (WHO, 2010). Even though the majority of emigrants build new lives where they take up residence, a small percentage of them return to their countries of origin. That small percentage is often responsible for innovations—advancing the adoption of existing technology and expanding the knowledge base—that would not otherwise have happened had they not been exposed to training environments abroad. In addition, Kangasniemi et al. posit that "returning migrants can transform the brain drain into a highly beneficial 'brain circulation' ...and while the returnees are not likely to work in the most impoverished rural areas, ...it is possible that their return 'pushes' other doctors out into the rural areas" (2007).

Unfortunately, since the government of Bangladesh will not employ physicians who emigrate from the country, there is no guarantee that Bangladeshi doctors trained overseas, no matter how well intentioned, can deliver care to the impoverished. Though government facilities exist to provide care to these marginalized citizens, the existing system has a number of drawbacks, the most pronounced of which is inefficiency:

There are simply too few doctors available to see the patients [who] wait exorbitant amounts of time before being [seen]. Additionally, funds are often insufficient or misappropriated, which results in half-constructed operation theaters or unmanned examination rooms in hospitals and clinics. As a result ... only 30 percent of Bangladesh's population utilizes the government's health services (Chaudhury, 2003).

In spite of the medical system's current state, my mother still believes that Bangladesh will be able to meet its healthcare gap. "How?" I asked her. "Activism," she replied. "We, the 'ex-pats,' have to negotiate at the government level. And we need to have access to teaching. We're not asking for money—we're volunteering." She insists that this will happen in my lifetime. Since Bangladesh established its independence in 1971, until 1990, physicians were not allowed to emigrate, meaning my mother's generation essentially trained and became established in developed nations. Because of this, many are willing to return to Bangladesh at some point in their lives to advance the existing medical knowledge and technology. Of course, this effort requires internal support, as well. Many of my mother's medical school classmates are involved in recruiting Bangladeshi physicians back home from overseas. Because they are established within the country, they may have power to circumvent policies that bar ex-patriate physicians

from making changes to Bangladesh's healthcare system. As Bradby noted, the emotive descriptors attached to the brain drain have often maligned the recruitment of trained health professionals by developed countries. But listening to my mother's story, it became clear that there are individual impulses to address brain drain as well; people sincerely want to give back to their native health systems. A study of South African health workers who had immigrated to the U.K., for example, found that those who had left to pursue academic opportunities were more likely to return to South Africa. Indeed, some had emigrated for the express purpose of gaining skills and expertise to apply in the South African health system (Bidwell et al., 2014).

"Is there a policy solution?" I asked her. After all, the prevailing mindset has been that strengthening domestic healthcare is necessary to retain domestic health professionals: improved conditions, fair remuneration, and education in resource-poor countries would allow health workers to function effectively and would also provide them with lasting social benefits (Mackey & Lang, 2013). Several different policy improvements have been suggested, including diversifying the skills mix to maximize the potential of non-physician health workers, and encouraging migrant workers to return to their home countries (Cometto et al., 2013). But my mother says that policy solutions would be ineffective for Bangladesh; the government de-incentivizes emigration by barring return (Rahman & Khan, 2006). In addition, the inefficacy of the existing government-run healthcare system seems to indicate that policy is the opposite of the solution. Although there has been a major shift in the government health policy during the last decade, one critic for the Global Health Watch notes that

such policy has not been based on the assessment of health needs of the population. For instance, health services, previously offered at the household level, [are now delivered] at the community clinics.... Introduction of user fees [at government facilities] has marginalized access for the poorer sections. Health services have been integrated at the community level without considering institutional constraints. Although this has been an attractive proposition, deep-rooted differences between different cadres of personnel have posed serious constraints to adequately provide services. These changes have considerable negative effects on health particularly among the ultra-poor (Hadi, 2004).

Indeed, many countries have attempted to de-incentivize emigration by imposing restrictions, and Bangladesh is merely one example. In addition, receiving countries have also attempted to implement ethical recruitment policies, for example, by sending compensatory payments to countries that have trained a significant portion of the destination country's healthcare staff (Bradby, 2014). But these policy changes have largely been ineffective. In the U.K., for instance, despite the adoption of the Code of Practice for National Health Service employers, which is designed to limit the recruitment of overseas health professionals to

the United Kingdom, active international recruitment by employers continued (Blacklock et al., 2012). In the United States, foreign medical graduates fill a vital gap in the health system: 58% of them are in primary care, a grossly underserved field, compared with only 27% of U.S. medical graduates (AMA, 2010). Indeed, foreign medical graduates are thought to perform a safety-net function by caring for the uninsured and indigent populations in inner-city and rural areas, in contrast to U.S. graduates (Mick et al., 2000).

But even with all the discussion of policy and politics, a more fundamental point was emerging from our discussion—in order for developing countries to advance, they need to import ideas from the outside, because "alongside the amplification of migration is the mobility of capital, ideas and technology" (Bradby, 2014). And my mother firmly believes that volunteer efforts, born out of a sense of loyalty to the country of one's birth, will provide the vehicle for healthcare in Bangladesh to move forward, little by little. "We're only going to add to the effort," my mother said. "The majority of it comes from inside. At the same time, though, Bangladesh can't just become the U.S. overnight. The primary factor is the lack of infrastructure."

Relying on the patriotism of ex-pats seems a little wishful, I remarked. After all, three quarters of the international medical graduates who train in the U.S. ultimately establish their practices here (AMA, 2010). In addition, there has been little formal exploration into the theory of "beneficial" brain drain; one of the few existing studies suggests that it is unlikely to be relevant in providing educational incentives to those seeking training in order to migrate (Kangasniemi et al., 2007). But my mom has faith: "People are emigrating all the time, from every generation. Some will establish their lives [in the U.S. or other developed countries], some will return to [their native country]. And if at some point, Bangladesh's infrastructure improves, such that it's comparable or even better to live there than [elsewhere]—then people will choose that." And in fact, it's already happening in some parts of the world. Indian-Americans from many sectors are moving back to India, where economic opportunities for returnees are on the rise, and quality of life is, in many respects, superior to the U.S. (Roy, 2009). Similarly, nearly a quarter of Lebanese medical students who intended to train abroad wished to return to their native country immediately after completing their training—perhaps more relevant to my mother's point, as Lebanon is considered a middle-to-high-income country with adequate infrastructure, existing health systems and economic stability to offer its healthcare work force (Akl et al., 2008).

Though brain circulation is a component in addressing brain drain, it is improbable that it will be a stand-alone solution. The factors that forced emigration of individuals to begin with, such as longstanding political instability and lack of infrastructure, are unlikely to be offset by a single-pronged approach. In order to truly address the brain drain, we must focus on at least three areas: brain circulation, encouraging return migration; "brain retention," incentivizing the retention of native health workers; and "brain banking," fiscal

commitment to the transfer and discovery of knowledge via funding, remittances and capital.

Although the return of native workers to address a nation's health crises is a lofty ideal, in reality, return migrants would be more likely to reside in affluent areas in which health needs are largely already met. An analogous problem, the "internal" brain drain of rural physicians to urban areas and from public to private sectors of developing countries, also remains to be addressed. In Malaysia and India, for example, many health workers have returned to work in the private sector, an often lucrative area due to medical tourism, but there is no evidence of these physicians working in the public sector. Again, the return migration of physicians to their home countries in these instances seems to fuel internal brain drain rather than brain circulation (Connell, 2011). Solely focusing on fostering return migration is actually likely to drive further public/private and urban/rural disparities rather than deliver care to the most needy. In response to these phenomena, Eyal and Hurst advocate the development of "locally relevant" medical curricula in underserved regional medical schools:

Students in a locally relevant medical school learn, for example, how to prescribe drugs that are more affordable for poor patients than the western standard of care (often generic equivalents) and that are safer to prescribe when supply or refrigeration are erratic. They gain true mastery in gleaning information using inexpensive tools like the physical exam. For example, they develop advanced expertise in stethoscope diagnosis, to a degree that Western physicians with access to expensive lab tests, X-ray and magnetic resonance imaging (MRI) usually do not require. These students become fluent at strategies and decision algorithms that might be irrelevant or grossly suboptimal in well-equipped Western settings, but remain highly recommended for scarcity conditions... Many rotations, or even the bulk of training, take place in rural and underserved communities, rather than city hospitals, and schools encourage admissions from members of these communities. The explicit aim of medical education is to prepare physicians primarily for work in underserved areas (Eyal and Hurst, 2008).

Locally relevant training, they argue, could make graduates' skills less marketable abroad. Similarly, such a system could boost the prestige of local practice, as well as focus recruitment in rural areas, thereby mitigating the internal brain drain by offering rural practitioners new career options in education and capacity building.

In addition to educational programs fostering brain retention, host countries must also invest in research and development, and in broader opportunities for science and education. For example, remittances from Bangladeshis living overseas amount to \$2 billion annually, the country's second largest source of foreign revenue. Brain banking funds such as these should be used to expand educational

opportunities for those residing within the country, which may promote retention of those who would otherwise seek better training and education abroad. In an alternate sense,

brain banking also includes expatriate scientists and healthcare professionals [who] can contribute their knowledge, clinical and research skills to their native countries by developing collaborative training programmes, research projects and teaching their own countrymen. This requires the commitment of foreign scientists and receptiveness at the other end (Dodani & Laporte, 2005).

Lastly, promoting brain circulation is likely the most complex of these problems. In many ways, the draw of improved infrastructure and job security in their native countries is the least of emigrants' concerns when considering return migration. In Africa, for instance, many emigrants want to return, and would be more likely to do so if official programs or organizations existed to help them with the process and logistics of re-establishing themselves. A number of prohibitive barriers exist for returning health workers. Working in the public sector is difficult, especially as one is often working below one's qualifications and pay or skill grade. Lack of recognition of qualifications also needs to be addressed with policy changes, and accounts abound from both Africa and Bangladesh, as have been summarized above (VSO, 2010).

Despite all of these barriers, however, there are physicians who return—permanently or periodically—to Bangladesh. Although little data is available on the rates of return migration to emigrant physicians' countries of origin, Bangladesh's unique historical context paves the way for brain circulation to occur. My mother's generation grew up and practiced largely outside the country, creating a small diaspora of expatriate physicians. This diaspora, as Omar Rahman points out, has the potential and the power to foster the transfer of social capital that can enhance economic growth and development of the homeland (Rahman, 2006). Rahman notes that the ability of diaspora members to do this hinges on several factors, including one that my mother had pointed out: the receptivity of the legal, political and bureaucratic structures in Bangladesh to such exchanges, either via the return of migrants or trans-nationals—the latter referring to those who move fluidly between homeland and destination country. Another necessity, Rahman writes, is the development of institutional frameworks and groups within the diaspora community that can specifically identify targeted areas in which coherent, long-term, sustainable transfer programs can be created.

To this latter point, there are a few organizations of Bangladeshi ex-patriate physicians in the U.S. One of these, the Bangladesh Medical Association of North America (BMANA), has sponsored journals for medical colleges in Bangladesh, as well as telemedicine projects that harness technology to deliver consultations, obviating the need to travel back to Bangladesh. Many, however, have also done exactly this—physicians from many specialties have traveled back to Bangladesh to give various lectures, and some have

even performed advanced cardiac procedures and established facilities that can house the resources to provide these services, which previously would have been impossible. In addition to providing education to Bangladeshi doctors-in-training, many diaspora physicians have provided *pro bono* services directly to patients, including in rural underserved areas (Rahman, 2006).

My mother, too, is a member of her medical school's alumni association, which annually sponsors the White Coat Ceremony for the entering class at Sallimullah Medical College. Her classmates periodically return to Dhaka to teach courses and to mentor students, and she hopes to have time to join this effort, too. And Sallimullah is not the only medical school with a generous and well-connected alumni base. One of my mother's colleagues in New York, a graduate of Dhaka Medical College, also travels back every few months to teach pathology courses and seminars there. To Rahman's point, organization is key—solidifying institutions that represent groups of ex-patriate physicians lends them credibility, negotiating power, and the resources to advocate at higher political and bureaucratic tiers.

Anecdotally, these combined efforts seem significant, but there is still much work to be done. In truth, the Bangladeshi Diaspora in the U.S. is not sizeable enough to eradicate health infrastructure disparities. BMANA, for instance, has only 300 active members. Remarkably, Rahman points out that “the eventual Bangladeshi Diaspora should include second and possibly third generation Bangladeshis... these individuals may have special ties to the birthplace of their parents even if they were not born there” (2006). Here, I realize, he's referring to me. In fact, as soon as I entered medical school I knew I wanted to experience the health-care system in Bangladesh for myself. I spent a summer at the Dhaka Medical College Hospital after my first year of medical school, and it was an experience that cemented my interest in global health, as well as my commitment to working in the health sector, particularly capacity-building, in Bangladesh. So perhaps my mother's hope is well-placed; the Bangladeshi Diaspora can grow if we can continue to nurture these cultural links.

But despite these current efforts, and although I agree with my mother that return migration could be a pivotal factor in combating the brain drain, the other issues of retention and economics must be targeted in unison. The exchange of ideas has to occur not only via physical migration of individuals, but by internal investment in the country's future. Barriers to this still exist—it is difficult for ex-patriate physicians and health workers to have a voice within Bangladesh's national health system, as no formal channels are in place, and as mentioned above, there are only a handful of formalized diaspora physician groups. In addition, the emotive nature of the debate may hold us back from seeing the true barriers—accusations directed at developed countries that actively recruit talent from the developing world do not advance the mission of change. Instead, incentives to return home and exchange programs to train physicians, would better foster the exchange and circulation of knowledge.

To reconcile my mother's point with my conclusions, it is not enough simply to exchange ideas—but it is an important component.

“Even if not in my lifetime, definitely in yours,” my mother says. “You'll see Bangladesh move forward. Lots of ideas will be exchanged.”

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An Uncommon Cause of Acute Abdominal Pain: Primary Epiploic Appendagitis in the Emergency Setting

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In the emergency setting, the diagnosis of benign causes of acute abdominal pain can prevent unnecessary medical interventions. To illustrate this point, we report the case of a 28-year-old man who presented to the emergency department with symptoms suggestive of acute diverticulitis. Abdominal computed tomography (CT) established, instead, a diagnosis of primary epiploic

appendagitis (PEA), which was managed expectantly. The patient's symptoms resolved within one week of hospital discharge and he remained free of pain at a five-month phone follow-up. Increased awareness of PEA and its self-limited course can help the emergency physician avoid unnecessary imaging studies and expectantly manage this cause of acute abdominal pain.

INTRODUCTION

Epiploic appendages are pedunculated pouches of subserosal fat, 1-2 cm in thickness and 0.5-5 cm in length, that line the external surface of the large intestine (Ross, 1950). These highly mobile structures have a limited blood supply and are susceptible to ischemia due to torsion or to *de novo* venous thrombosis of the vascular stalk anchoring them to the surface of the large intestine. The inflammation resulting from this ischemia precipitates epiploic appendagitis, which can be primary or secondary (Rioux & Langis, 1994; Singh, A.K. et al., 2005; Sand et al., 2007). Primary epiploic appendagitis (PEA) occurs spontaneously, while secondary epiploic appendagitis (SEA) is the result of a pre-existing abdominal inflammatory process occurring adjacent to the affected epiploic appendage (Vriesman et al., 2003; Rioux & Langis, 1994; Vinson, 1999). Pathophysiologically, PEA or SEA are characterized by a cascade of ischemia, infarction and aseptic fat necrosis that results in clinical symptoms. Due to the presence of epiploic appendages along the entire length of the large intestine, these clinical symptoms tend to be nonspecific and closely mimic other causes of abdominal pain (Legome, 2002; Lien et al., 2004; Rioux & Langis, 1994).

CASE PRESENTATION

We report a case of a 28-year-old male who presented to the emergency department with "sharp" left lower quadrant abdominal pain that began three days prior. Although the patient reported the pain to be 8/10, it was notable that he appeared to be in no acute distress. He denied nausea and vomiting, and denied changes to his appetite and bowel habits. His past medical history was noncontributory. Collected vital signs were as follows: oral temperature 98.5°F, heart rate 81 bpm, blood pressure 158/79 mmHg, respiration rate 18 respirations/minute and oxygen saturation 97% (room air). Physical examination revealed tender-

ness and guarding in the left lower quadrant. Urinalysis, complete blood count, comprehensive metabolic panel and serum amylase/lipase values were normal, except for a mild leukocytosis ($10.9 \times 10^3 / \text{mm}^3$). A contrast-enhanced abdominal computed tomography (CT) imaging study was obtained, which revealed a normal appendix and the absence of diverticula. Instead, CT images of the sigmoid colon demonstrated an ovoid, fatty structure with a dense rim that displayed mild fat stranding consistent with a diagnosis of PEA (Figure 1A, Figure 1B). Soon thereafter, the patient was discharged with pain medication for symptom management and was told to return to the emergency department if the pain worsened. During a phone follow-up conducted five months after his presentation to the emergency department, he reported that his abdominal pain resolved completely one week following hospital discharge and had not returned.

DISCUSSION

PEA was once considered a rare surgical diagnosis, but its true incidence has recently been called into question (Almeida, 2009). Before the widespread use of abdominal CT imaging, PEA was frequently misdiagnosed as diverticulitis because of its predominance in the rectosigmoid junction. As this misdiagnosis indicated medical, rather than surgical, management, the correct diagnosis of PEA was obscured and its true incidence falsely diminished (Ghahremani, 1992; Carmichael, 1985; Molla, 1998; Almeida, 1999; Rao, 1998). Today, abdominal CT and ultrasonography have made the diagnosis of PEA more frequent with reports demonstrating PEA to be the diagnosis in two to seven percent of cases of acute abdominal pain when diverticular disease was suspected, and in one percent of cases of acute abdominal pain when appendicitis was suspected (Vriesman, 2002; Zissin, 2002).

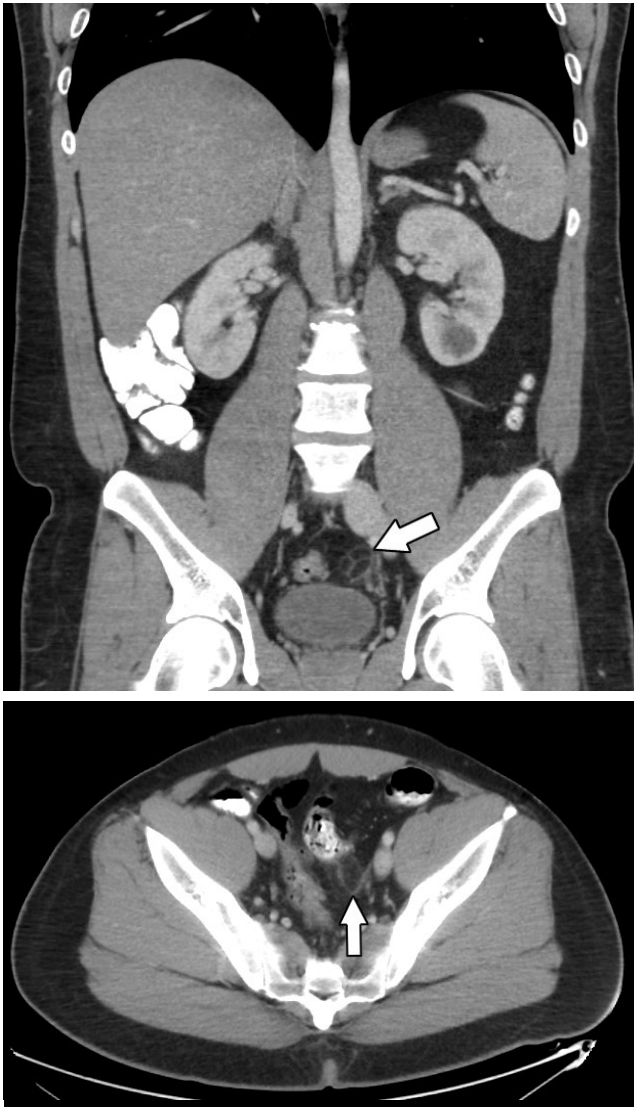


Figure 1 | (A) Axial CT image with hyperattenuating ring sign (arrow). (B) Frontal CT image with hyperattenuating ring sign (arrow).

The mean age of diagnosis of PEA is 40 years of age, and men may be more often affected by PEA than women (Sand et al., 2007; Jain et al., 2008; Rioux & Langis, 1994; Ozdemir et al., 2010; Hollerweger et al., 2002). Physical exertion or an extreme stretching movement of the abdomen has been reported to be a predisposing factor in the development of PEA (Ghahremani et al., 1992; Jennings & Collins, 1987; Ross, 1950; Rioux & Langis, 1994). Although epiploic appendages are present along the entire length of the large intestine, published reports suggest that 57% of PEA cases affect the rectosigmoid junction and 26% of cases affect the ileocecal region (Legome et al., 1999; Sangha et al., 2004; Hiller et al., 2000). An inflamed epiploic appendage in these locations produces a sharp, focal, non-migratory abdominal pain that can easily be mistaken for diverticulitis, appendicitis or acute cholecystitis (Boulanger et al., 2002; Schnedl et al., 2011). Patients are predominantly afebrile and do

not usually have gastrointestinal symptoms such as nausea, vomiting, anorexia or changes in bowel habits (Legome et al., 2002; Sangha, 2004). Physical examination is usually notable for focal tenderness localized over the site of inflammation (Rioux & Langis, 1994). Laboratory values are usually within normal limits, but a slight leukocytosis and a mildly elevated serum C-reactive protein may be seen (Rioux & Langis, 1994; Ozdemir et al., 2010; Sand et al., 2007; Ozkurt et al., 2007; Sandrasegaran, 2004).

The diagnosis of PEA relies on abdominal CT or ultrasonography—diagnosis based on symptoms alone is essentially impossible (Schnedl et al., 2011). PEA can be diagnosed on abdominal CT images by the “hyperattenuating ring sign” (Vriesman, 1999; Rioux & Langis, 1994). This sign, considered diagnostic for PEA, consists of an approximately 3 cm fatty, ovoid mass bound by a thick ring of hyperattenuation located near the colon (Figure 1A, Figure 1B). The ring may also contain a centralized hyperattenuating dot, presumably representing the thrombosed and necrotic vessel that once supplied the appendage. Evidence of fat stranding may also be seen in the vicinity of the lesion (Vriesman, 2003; Danielson et al., 1986).

The diagnostic finding of PEA on abdominal ultrasonography is the visualization of an ovoid, paracolic mass that is hyperechogenic and noncompressible, and is usually attached to the anterior parietal peritoneum (Rioux & Langis, 1994; Jennings et al., 1987; Hollerweger et al., 2002). The mass is often surrounded by a hypoechoic border, which corresponds to the hyperattenuating ring sign found on CT imaging (Vriesman, 2003; Rioux & Langis, 1994). Ultrasonography is particularly useful in the diagnosis of PEA because the sonographic findings can be directly correlated to the patient’s point of maximal tenderness and because the inflamed appendage’s adherence to the peritoneum can be easily demonstrated upon deep inspiration and expiration by the patient (Hollerweger et al., 2002).

PEA is usually a self-limited condition that can be managed expectantly with anti-inflammatory medications, or surgically by laparotomy (Apakama et al., 2011). Managed expectantly, symptoms generally resolve between three and 14 days, although future recurrences are possible (Fraser et al., 2009; Apakama et al., 2011). Patients should be counseled to return for surgical excision of the affected appendage if their symptoms persist, as this is considered the only definitive cure (Apakama et al., 2011; Rioux et al., 1994; Schwartz et al., 1994). Although rare, adverse outcomes of expectantly managed PEA have been reported and include abscess formation, bowel obstruction, intussusception, peritonitis and death (Romaniuk et al., 1993; Shamblin et al., 1986; Puppala et al., 1981; Murdie, 1953; Ghahremani, 1992; Apakama, 2011). Our patient presented with characteristic symptoms of PEA: a sharp, well-localized non-migratory pain in the left lower quadrant without additional gastrointestinal symptoms. Although initial imaging with ultrasonography would have been preferable, the discordance between this patient’s clinical presentation and his age raised our suspicion of a more insidious etiology,

and so an abdominal CT study was ordered. His symptoms resolved completely with expectant management within the time range reported in the literature and had not returned at a five-month phone follow-up.

While once thought of as a rare diagnosis, PEA should be part of the emergency physician's differential diagnosis in patients presenting with acute abdominal pain. The use of ultrasonography as an initial imaging method for these patients can help physicians rapidly diagnose PEA, avoid unnecessary further imaging and expectantly manage this benign condition successfully.

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Acute Obstructive Suppuration of the Pancreatic Duct Causing Sepsis

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Objective: We report a rare case of acute obstructive suppuration of the pancreatic duct causing sepsis, which was successfully treated with emergent endoscopic retrograde cholangiopancreatography (ERCP).

Methods: We describe the patient's clinical presentation, laboratory test results, and imaging used for diagnosis and treatment.

Results: A 33-year-old female with a history of recurrent acute pancreatitis was admitted during an episode of acute pancreatitis. Computed tomography (CT) scan of the abdomen revealed acute pancreatitis, diffuse pancreatic atrophy and pancreatic ductal dilatation with obstruction due to a soft tissue lesion within the distal duct. Shortly after admission she developed symptoms and signs of sepsis. Urgent ERCP was performed to further assess the suspected cholangitis. "Clean" bile emanated from the common bile duct, while copious purulent

fluid was detected at the dilated pancreatic duct orifice, confirming suppuration of the pancreatic duct. A plastic single pigtail stent was placed traversing the ampulla and pancreatic duct stones that were causing the obstruction, which were later removed. After endoscopic decompression, the patient rapidly improved over the following 24 hours and had no subsequent admissions for pancreatitis.

Conclusion: Acute suppuration of the pancreatic duct (ASPD) is a rare and potentially fatal infectious complication of pancreatic ductal obstruction with few cases reported in the English literature. It would be of interest to further investigate the exact pathophysiology leading to development of ASPD. The endoscopic methods of urgent ERCP and pancreatic duct decompression utilized in our case proved effective in successfully treating ASPD. This unusual condition should be considered in patients with acute pancreatitis who develop early clinical decompensation.

INTRODUCTION

Pancreatic abscess, necrosis, and pseudocyst are well-known entities that can complicate pancreatitis and lead to pancreatic sepsis (Sarr et al., 2013; Deeb et al., 2008). Acute obstructive suppurative cholangitis is a common clinical entity. However, pancreatic duct (PD) obstruction and acute suppuration of the pancreatic duct (ASPD) leading to sepsis, without a concurrent pancreatic abscess or infected pseudocyst, is an extremely rare complication with few cases reported in the English literature (Fujimori et al., 2011; Tajima et al., 2006). In ASPD, pancreatic obstruction results in the development of infection and pus within the PD, leading to sepsis. Here, we report a case of ASPD successfully treated with emergent endoscopic retrograde cholangiopancreatography (ERCP).

CASE

A 33-year-old female with a past medical history of recurrent acute pancreatitis, likely secondary to tropical pancreatitis, presented with a one-day history of severe epigastric pain radiating to the back. Pain was sharp, 7/10 in intensity, and associated with nausea. No fever or chills were reported. She denied alcohol consumption, smoking, illicit, herbal or prescription drug use, or any other significant medical history. She reported multiple episodes of pancreatitis in the past and had previously undergone ERCP and cholecystectomy at an outside hospital.

On presentation, the patient was afebrile, blood pressure (BP) 137/90 mm Hg, heart rate 70 beats per min, respiration rate 18 breaths per min, and body mass index of 19.8 kg/m². On physical examination her abdomen was soft, non-distended, tender in the epigastric area, with guarding but no rebound tenderness. Normal bowel sounds were present. The remainder of the physical examination was unremarkable. Laboratory testing revealed a white blood cell (WBC) count of 8.3 K/ μ L and normal pancreatic enzymes with an indirect hyperbilirubinemia (1.6/0.2 mg/dL). Ultrasound of the abdomen demonstrated common bile duct (CBD) dilatation of 7 mm, consistent with a post-cholecystectomy state. Computed tomography (CT) scan of the abdomen, with per os and intravenous (IV) contrast, revealed acute pancreatitis (AP), diffuse pancreatic atrophy and pancreatic ductal dilatation (Figure 1) with obstruction due to a soft tissue lesion within the distal duct (Figure 2). The patient was clinically stable upon admission and was treated with bowel rest, pain management and aggressive IV hydration.

Within the next 24 hours, the patient developed leukocytosis (WBC 15.5 K/ μ L, neutrophil count 92.4%), hypotension (BP 90/51 mm Hg), fever (maximum temperature 101.2° F) and chills. Obtained blood cultures showed no growth after five days. Emergent ERCP was performed. The major ampulla appeared edematous and a previous sphincterotomy was noted. The CBD was cannulated, nonpurulent bile ema-

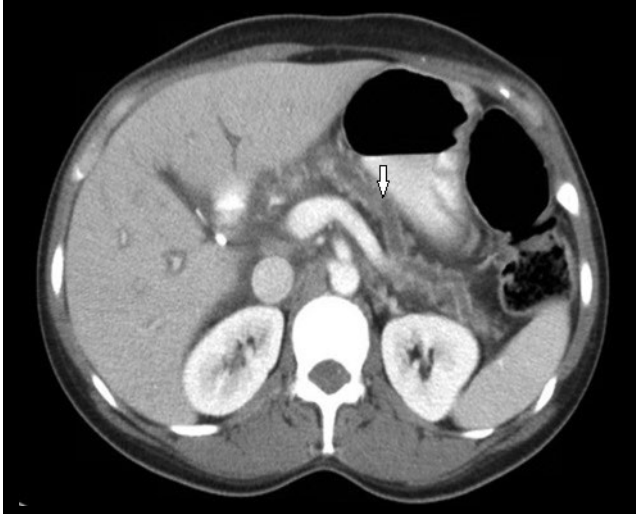


Figure 1 | Diffuse pancreatic ductal dilatation (arrow).

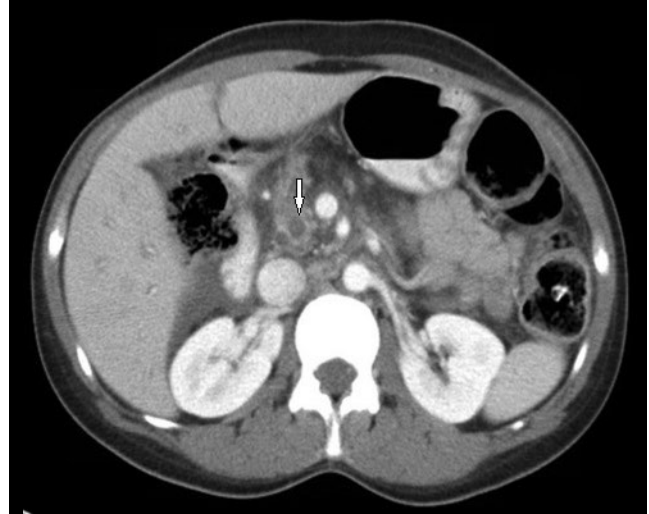


Figure 2 | Soft tissue lesion (arrow) within the distal duct.

nated and cholangiogram did not reveal biliary obstruction. After pancreatic ductal cannulation, copious purulent fluid emanated from the orifice (Figure 3); however, due to the viscosity of the purulent fluid it could not be aspirated or cultured. A pancreaticogram revealed diffuse PD dilatation and multiple filling defects, consistent with stones. A plastic single pigtail stent was placed traversing the ampulla and PD filling defects. Purulent fluid drained from the stent, and was followed by clear pancreatic fluid. The patient rapidly improved over the following 24 hours. Prior to discharge, she underwent ERCP with pancreatic ductal sphincterotomy, multiple stone extraction (Figure 4), and pancreaticogram, which revealed no further filling defects. The remainder of the patient's hospital course was uneventful and she was discharged home. She followed up with the outpatient clinic and had no subsequent re-admissions over the next twelve months.

DISCUSSION

Complications of acute pancreatitis are well known and include pseudocyst formation, pancreatic necrosis, and multisystem organ failure (Sarr et al., 2013; Deeb et al., 2008). Acute pancreatitis is also a risk factor for the development of chronic pancreatitis. Patients with chronic pancreatitis may suffer from chronic pain, exocrine deficiency and diabetes (Forsmark, 2013). Acute suppuration of the pancreatic duct is a rare but significant complication of chronic pancreatitis. ASPD develops due to obstruction of the pancreatic duct resulting in fluid and bacterial stasis (Deeb et al., 2008). Similar to ascending cholangitis, the pancreatic duct fills with pus and the patient quickly decompensates. The treatment of choice is resuscitation, broad-spectrum antibiotics and emergent endoscopic decompression (Fujimori et al., 2011; Tajima et al., 2006).

Risk factors for the development of ASPD have been suggested in the literature. A single culprit microorganism was identified in each of the three previously reported cases. The microorganisms were *Klebsiella ornithinolytica* (Deeb

et al., 2008), *Stenotrophomonas maltophilia* (Fujimori et al., 2011), and *Escherichia coli* (Tajima et al., 2006). While Weinman reported a case of ASPD, the culprit microorganism was not identified (Weinman, 1995). Risk factors thought to contribute to the development of ASPD in these previously reported cases included diabetes, post-transplant immunosuppression, and malignancy. Although conclusive evidence of bacterial infection via positive blood cultures is not available in this case, we strongly believe the patient's clinical presentation of fever, hypotension, leukocytosis, and purulent discharge from the pancreatic duct, and her improvement after intravenous antibiotics and emergent ERCP, suggest a bacterial etiology that contributed to sepsis.

Marotta et al. noted that patients with chronic pancreatitis were more susceptible to infections, likely due to impaired antibacterial activity of the pancreatic secretions, as compared to those with a normal pancreas (Marotta et al., 1997).



Figure 3 | Pus traversing the pancreatic duct orifice.

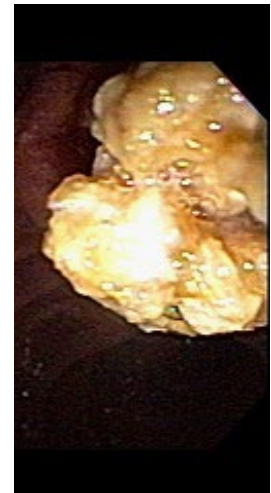


Figure 4 | Large stones from the pancreatic duct.

In 1968, Williams and Byrne demonstrated that injection of bacteria into the pancreatic duct was not sufficient by itself to cause pancreatitis (Williams & Byrne, 1968). Tropical pancreatitis (a type of chronic pancreatitis), history of prior sphincterotomy, and intraductal pancreatic stones (especially if they are also obstructing the outflow of the duct), contribute to ductal infection. Duodenal contents may reflux into the biliary tree or pancreatic duct after sphincterotomy, particularly if the patient has a common biliary and pancreatic sphincter (Weinman, 1995). In the case presented here, risk factors that likely contributed to the development of ASPD included history of prior sphincterotomy, chronic pancreatitis, and pancreatic ductal obstruction by a calculus.

ASPD is a rare and potentially fatal infectious complication of pancreatic ductal obstruction. This unusual condition should be considered in patients with acute pancreatitis who develop early clinical decompensation. It would be of interest to further investigate the exact pathophysiology leading to development of ASPD. As in this case, emergent ERCP and PD decompression are essential in the successful treatment of ASPD.

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Bithalamic Dysfunction in Wernicke's Encephalopathy

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We describe a 65-year-old, nonalcoholic, right-handed female with multiple vascular risk factors who developed transient visuospatial hemineglect and global aphasia after presenting with the classic triad of Wernicke's encephalopathy (mental status changes, nystagmus/ophthalmoplegia, and ataxia). A brain MRI showed no evidence of acute infarction, but demonstrated signal

change in the medial thalami and mammillary bodies. Intravenous thiamine therapy was given, and visuospatial hemineglect and ophthalmoplegia disappeared while the aphasia improved. The occurrence of these acute transient clinical features has not been previously reported in Wernicke's encephalopathy.

A 65-year-old, nonalcoholic, right-handed female with hypertension, diabetes, hyperlipidemia, and a history of ischemic strokes with residual right-sided hemiparesis initially presented with nausea, vomiting, poor oral intake and a 43-kg weight loss (25% of baseline weight) over several weeks. On admission, she received a continuous intravenous glucose infusion. Four days later she developed disorientation. On initial evaluation, she did not exhibit neglect, but was observed to be inattentive and only followed simple requests. The patient was oriented only to her name and identified few simple objects. Further examination revealed binocular abduction paresis with nystagmus, bilateral upper limb dysmetria, and mild residual right-sided hemiparesis. A clinical diagnosis of Wernicke's encephalopathy was made and she was given intravenous thiamine at 1500 mg/day. However, on the following day, the patient was unable to express, comprehend or repeat language (global aphasia). Her gaze deviated to the right and she only attended to examiners on the right side, not on the left (profound visuospatial neglect). Although significant inattention was present, she followed simple requests at times, and her language deficit was constant and out of proportion to inattention. She had notably decreased limb movement on the left side, even in comparison to her previously known right hemiparetic side. The patient did not withdraw, regard, or visually track noxious stimuli in the left arm, which we interpreted as another sign of visuospatial hemineglect on the left side. Seven hours after examination, a brain MRI obtained to rule out an acute stroke showed no evidence of acute infarction (diffusion weighted imaging MRI was negative) and instead demonstrated typical MRI findings for Wernicke's encephalopathy, including signal change in the medial thalami and mammillary bodies (Figure 1). Intravenous thiamine therapy was continued and, three days later, visuospatial hemineglect and ophthalmoplegia abated while aphasia improved. Intravenous thiamine was reduced to 500 mg/day. After seven days of intravenous thiamine therapy, she was transitioned to oral thiamine at 100 mg/day. Two weeks into thiamine therapy, the patient was fully oriented, speaking fluently and following all requests.

Extensive gastrointestinal work-up revealed gastroesophageal reflux disease, gastritis/duodenitis, and gallstones with chronic cystitis. The patient required total parenteral nutrition for several days, but gradually tolerated an oral diet. She was discharged on oral thiamine at 100 mg/day.

DISCUSSION

Wernicke's encephalopathy is characterized by a triad of mental status changes, nystagmus or ophthalmoplegia, and ataxia due to thiamine (vitamin B1) deficiency (Sechi & Serra, 2007). The syndrome occurs due to selective dysfunction of brain regions including the thalami, mammillary bodies, pontine tegmentum, abducens and oculomotor nuclei, and cerebellum. Our patient initially presented with the classic triad of Wernicke's encephalopathy. This was followed by onset of unexpected visuospatial hemineglect on the left side and global aphasia, leading us to suspect a stroke. A brain MRI revealed classic radiographic findings of Wernicke's encephalopathy, including signal changes in the medial thalami and mammillary bodies (Zuccoli & Pipitone, 2009) and confirmed the diagnosis. It is well known that additional neurologic signs including hyperthermia, increased muscle tone, paresis, choreic dyskinesias, and coma may appear a few days after the onset of initial symptoms (Sechi & Serra, 2007). However, a transient appearance of dense visuospatial hemineglect or global aphasia has not been previously reported. We speculate that this may have been caused by a transient dysfunction of the bilateral thalami, given the striking signal alteration in this region on MRI. Dysfunction of the right thalamus can cause visuospatial hemineglect on the left side (Bogousslavsky, Regli, & Uske, 1988; De Witte et al., 2011; Watson & Heilman, 1979), and dysfunction of the left thalamus can cause aphasia (Bogousslavsky et al., 1988; De Witte et al., 2011; Kumar, Masih, & Pardo, 1996). For example, in the literature a case has been described where a patient with deep cerebral venous thrombosis with bithalamic infarction presented with a transient left-side visuospatial neglect, aphasia and amnesia (Benabdeljlil et al., 2001), which resembles our case. Another consideration is our patient's prior history of lacunar infarcts in subcor-

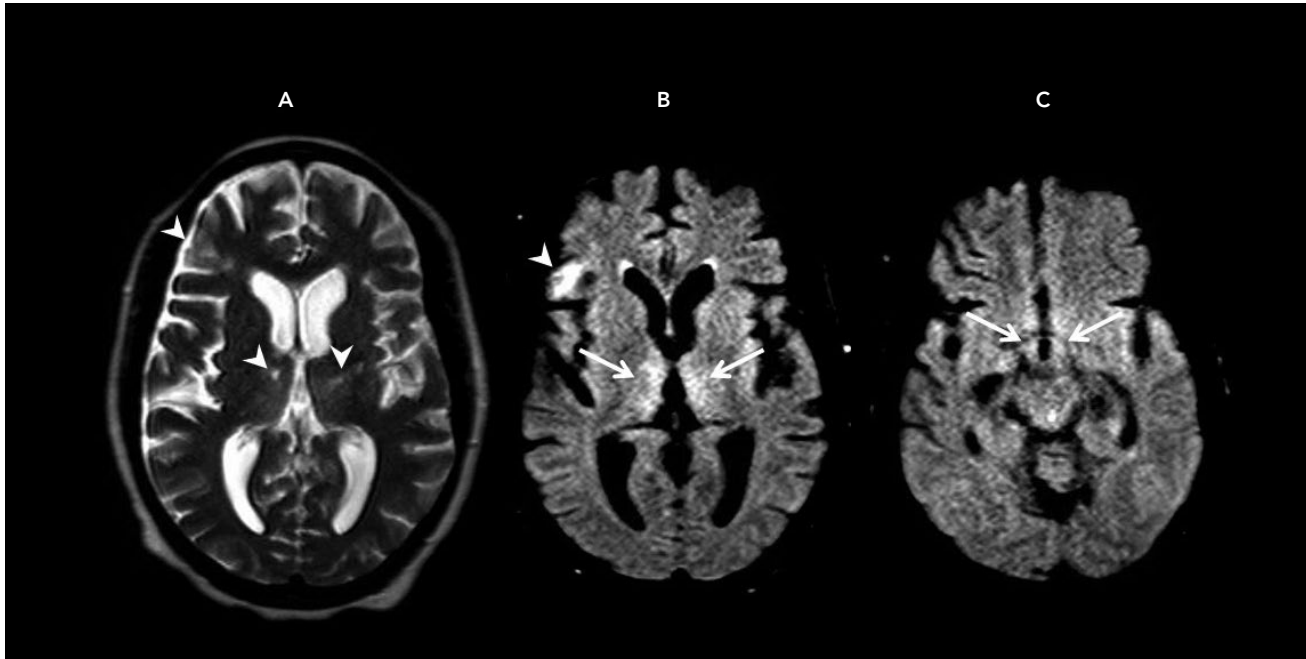


Figure 1 | (A) Axial T2 weighed image shows chronic lacunar infarcts in the right frontal operculum and thalami (arrowheads). (B) Axial FLAIR image reveals hyperintensities in the bilateral paramedian thalami (arrows). An old lesion from ischemic stroke is seen in the right frontal operculum (arrowhead). (C) Axial FLAIR image shows signal intensity alterations of mammillary bodies (arrows).

tical structures, including the bilateral thalami and the left corona radiata, resulting in residual right-sided hemiparesis. Thus the patient's remaining thalamic function may have been more vulnerable to transient metabolic insults related to thiamine deficiency, and her symptoms could have partially stemmed from an anamnestic response to old lacunes in the thalami. Transient gaze deviation and aphasia could be ictal or post-ictal phenomena, but we did not obtain an EEG on this patient since we felt her series of symptoms were not epileptic in nature. In elderly patients, Wernicke's encephalopathy can be seen in a nonalcoholic setting and can present with atypical features, possibly modified by multiple medical comorbidities.

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Nonketotic Hyperglycemic Chorea-Ballism (NKHCB): An Atypical Case and a Review of Literature

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Nonketotic hyperglycemic chorea-ballism (NKHCB) is a rare movement disorder characterized by hemichorea-hemiballism, contralateral striatal abnormality, and rapid resolution following glycemic control. We describe an atypical case of NKHCB in a 71-year-old female with uncontrolled type 2 diabetes exhibiting hemichorea and hemiballism limited to the right upper extremity. While NKHCB patients typically show abnormalities on com-

puted tomography (CT) imaging of the head, a CT scan of our patient during the acute phase was unremarkable. The movements subsided following glycemic control and fluid administration. The current literature on NKHCB is sparse and largely limited to case reports and series. We discuss several typical and atypical presentations and findings on imaging.

INTRODUCTION

Nonketotic hyperglycemic chorea-ballism (NKHCB) is a rare movement disorder typically associated with uncontrolled type 2 diabetes (Lai et al., 1996), though a few cases have also been reported in the setting of type 1 diabetes (Hashimoto et al., 2012). NKHCB is characterized by hemichorea-hemiballism that resolves rapidly following glycemic control. Isolated cases of more generalized, atypical, and unremitting disorders have also been reported (El Otmani et al., 2009; Massaro et al., 2012).

We describe a case of NKHCB limited to the right upper extremity that did not show any detectable abnormalities on computed tomography (CT) imaging.

CASE REPORT

A 71-year-old female with past medical history significant for poorly controlled type 2 diabetes, hypertension, hyperlipidemia, coronary artery disease, and a cerebral vascular accident without residual deficits, presented to the Jacobi Medical Center emergency department for acute onset of right upper extremity involuntary movements. The patient was in her usual state of health and was watching television at home when she noticed a fine tremor of her right upper extremity. The tremor worsened with intentional movement of the arm. Although the patient initially denied ballismic movements, she later recalled her arm having a "mind of its own." The movements kept her awake all night and prompted her to visit the hospital. She denied any numbness or weakness, but had difficulty holding objects in her right hand due to the movements. Except for a mild headache, she had no other complaints and the neurological exam was otherwise normal.

On examination, the patient was noted to have a kinetic and postural tremor punctuated by involuntary hemiballismic movements when the right arm was at rest. The patient reported being noncompliant with her insulin regimen and was found to have a serum glucose of 711 mg/dL (normal <180mg/dL) and HbA1C of 11.5% (normal <6.5%) on

testing. Her motor symptoms resolved within a couple of hours with correction of the hyperglycemia and with fluid hydration.

A head CT (Figure 1) showed mild cerebral atrophy and chronic small vessel ischemic changes. However, no evidence of a mass, mass effect, hydrocephalus, intracranial hemorrhage, acute segmental infarct, or extra-axial fluid collection was noted. Magnetic resonance imaging (MRI) was not performed due to the rapid resolution of the patient's symptoms.

The patient was discharged home on a regimen of pre-meal insulin lispro and nightly insulin glargine for long-term glycemic control.

DISCUSSION

Chorea-ballism is a poorly understood disorder with a diverse etiology and variable pathoanatomic findings (Dewey & Jankovic, 1989). The underlying pathophysiology also remains uncertain. A recent study of the acute phase and remission of 18 patients with NKHCB found strong evidence of reversible basal ganglion involvement. However, findings on T2W1 MRI were more variable and elevated Choline/Creatinine (Cho/Cr) ratios during remission suggested a more permanent neuronal change (K. Chang et al., 2010). Autopsy studies performed on patients with NKHCB have found ischemic changes of the basal ganglia, with one study also reporting calcification and mineralization (Nath, Jambhekar, Rao, & Armitano, 2006; Ohara, Nakagawa, Tabata, & Hashimoto, 2001). Positron emission tomography (PET) and single-photon emission computerized tomography (SPECT) studies similarly showed hypofunction of the striatum, suggesting a role for regional metabolic dysfunction secondary to hyperglycemia and vascular insufficiency (M. Chang, Li, Lee, & Men, 1996; Hsu, Wang, & Hsu, 2004).

In a retrospective report of 25 patients diagnosed with NKHCB at five Korean university hospitals between 1995 and 2010, six patients underwent a CT of the head, of which



Figure 1 | A head CT during the acute phase of the patient's NKHCB showed mild cerebral atrophy and chronic small vessel ischemic changes. No characteristic hyperattenuation of the basal ganglia was detected.

five showed contralateral hyperattenuation of the basal ganglia. The sixth patient had bilateral upper extremity ballismus with both CT and MRI of the head showing non-specific changes (Lee et al., 2011). Similarly, in a case series of three NKHCB patients who underwent CT imaging, two exhibited contralateral lesions of the basal ganglia, while the third patient, who had generalized chorea with no ballismic components, had no obvious abnormalities (El Otmani et al., 2009). Other patients with bilateral involuntary movements exhibit symmetric hyperattenuation of the lentiform nuclei on both CT and MRI imaging (Massaro et al., 2012).

CONCLUSION

NKHCB is a rare movement disorder that is not well understood. This case provides further evidence that clinical and radiological findings in NKHCB are variable, and adds to our understanding of NKHCB disease development and pathophysiology.

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The Burden of Shame

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Last fall, I spent four weeks working at an HIV clinic in Calcutta. The clinic was not so much an office as it was one giant room, like a rural schoolhouse. The doctors sat at the head of the room and called patients one by one from a waiting area of wooden benches. I sat with the doctors, looking out at the crowd.

"Why are most of the patients women?" I asked my preceptor.

I was taken aback by her answer. "The men have died. Most people in this country do not know about HIV. The women only get tested after their husbands fall ill or succumb to AIDS." The men are typically the first to become infected with HIV before passing it on to their wives, and thus show symptoms earlier, on average.

The patient we called next, though, was a thin, mustachioed gentleman, wearing the finest clothes he owned. He sat down and handed over the medical records he brought with him. In India, all patients with HIV carry a booklet with them tracking their CD4 lymphocyte counts (a marker of immune status) and antiretrovirals. He was not the patient; he had come as a surrogate for his wife, who was too ill to leave the house. The volume of patients was high, the afternoon was getting late, and the patient was not before us, so we refilled her medications, ignoring the reason for her absence.

I packed up to leave, and heading out I noticed this same man lingering by the exit.

"Wait," he asked with trepidation. "Will you look through these records again?" I explained that I was only a medical student, but my attempts to deflect him were unsuccessful. The records were all in English, he explained, and he just wanted someone to read them, to help him understand why his wife was so ill despite full compliance with her medications. Flipping through his wife's records, a grim tale of the last two years flashed before me. Despite an initial response to antiretrovirals, her CD4 counts kept dropping over the last year, finally bottoming out at 77. She lost a third of her body weight in six months, and one eye to Cytomegalovirus (CMV) retinitis. Still, no one made any changes to her antiretrovirals, except to add valganciclovir to her regimen. I am unsure why he trusted me. Perhaps it was because I took the time to read his wife's chart; perhaps it was because he was desperate to make someone, anyone care about his wife as she deteriorated in front of his eyes. Regardless, he asked me to come to his house in rural Calcutta, about an hour outside the city. I recognized the name of the village, as it was only ten minutes away from my uncle's house. I agreed to see him and his wife a few weeks later when I would be visiting my uncle.

I am ashamed to admit that at that time, I had made several assumptions about this man, whom I will refer to as Mr. Sen. I assumed he had HIV. I assumed he had an extramarital affair. I assumed he gave her the virus. I assumed he was showing such concern for his wife because he was consumed with guilt. I was wrong. Last year, his daughter became pregnant. On routine obstetric screening, she was found to be HIV positive, a shock to the entire family. Upon testing other family members, her mother was found to be positive for HIV antibodies, while her husband and her father both tested negative. Presumably, she contracted HIV via vertical transmission from her mother during birth. The question, then, became how did her mother get HIV in the first place 18 years ago? The assumptions I made about Mr. Sen paled in comparison to the gossip that circulated amongst the doctors while attempting to answer this question. "She got HIV and it wasn't from her husband. What kind of woman must she be?" "She must be hiding something. What did she do before she got married?" "She's a liar. A cheat. A whore."

A few weeks later, I made the journey out to my uncle's house. On a quiet Sunday evening, I walked over to the Sen household as promised. I asked neighbors until I zeroed in on a modest abode with cow dung drying on the walls. Mr. Sen came out to greet me. I took off my shoes and entered their one-room house. They lived in a communal home, sharing an outhouse and kitchen with the extended family. I sat on the edge of their bed, not quite knowing what to do next or why I was even there. Mrs. Sen, luckily, did not give me the opportunity to stammer my way through an awkward introduction.

"I'm not a bad person, you know." She spoke quickly, as if there was urgency and a need to voice her story immediately. "I know what everyone says about me. I know they think I have been unfaithful. But 20 years ago, right before I was pregnant with my daughter, I was very anemic, and I had to get iron shots. I remember they did not change needles between each patient, but I never said anything. I think that's when this happened to me."

Whether this was how she contracted HIV can never be verified, nor should it matter at this point. As doctors, we are well versed on the statistics, demographics and exposures associated with HIV infection. These epidemiological parameters have important implications for public health and aid in assessing the pre-test probability of HIV infection, but probing for the specific event leading to contraction of the virus only serves to assign blame and satisfy our lurid curiosity. However, Mrs. Sen insisted on sharing her story, because although having HIV was shameful enough for her, certain modes of transmission carried an even greater stigma.

At that moment, Mrs. Sen's daughter entered the room with her husband and other extended family. They had heard a "doctor" was at their house and rushed over to have their questions answered. Over the next half hour, I answered, in broken Bengali, questions ranging from the minutiae of how to reschedule a doctor's appointment to the complexity of how the virus causes opportunistic infections. Referring to Mrs. Sen's daughter, one of the family members asked, "How did she get HIV?" The question was innocent, but the tension amongst those that already knew the answer was palpable. I answered the question as non-specifically as possible, giving more of an overview of the different modes of transmission.

After the extended family had left, Mrs. Sen explained her trepidation. "My daughter, her husband, and my husband know I have HIV, but nobody else does." With a touch of panic in her voice, she implored, "Please don't tell them." "The other villagers, they know something is wrong," she continued. "They know I've gone blind. But they don't know why. They already stopped coming by our house. I'm afraid of what will happen if they learn the truth."

Controlling the network of people privy to her HIV diagnosis was a central theme in Mrs. Sen's life. She tried to strike a precarious balance—informing those that were affected by her disease, but hiding her illness from all others, even if they were within the family. It was exhausting for me to keep track of who knew what, and I can only imagine how difficult it must be to maintain that web of secrecy and trust.

By this time, it had been over an hour since I had been in their room, unusually long for a visitor to the Sens. It was a small community, and gossip had apparently spread that I needed to be rescued. Thinking I had been pressured into entering this house of disease, they came out of goodwill to provide me an escape. I was actually already wrapping up, so I made my exit a few minutes later. On the way back to my uncle's house, I was rebuked. "Why did you have to go in there? They aren't clean, you know." We got to a water pump, and I was made to scrub my hands thoroughly, as if I were a child caught playing in the dirt. By simply having interacted with the town pariahs, I had carried out of the house some of their stigma. I was tainted by whatever was in their air. Most importantly, I had broken the barrier they constructed out of fear and ignorance to protect themselves against this mysterious malady. The stigma I held, though, was ephemeral and easily washed away with soap and water, a luxury not afforded to this family.

The reaction of the villagers was all too common, and exactly the type of response Mrs. Sen feared. Petrified to go out and embarrassed to invite people in, Mrs. Sen had quarantined herself in her one-room home. This solution, obviously, was unsustainable, as solitude takes its own toll on the human spirit. I realized the reason I was called to their home was not to showcase the medical acumen I did not yet possess, but to serve as a human witness to her plights and a validation of her character. Before I left, she told me in a tone of resignation that now that her daughter was married, she could die peacefully. She was grateful for her husband, who continued to fight and seek medical care on her behalf, but she herself had given up, paralyzed by the indignity she would face outside the home. Even going to the doctor was embarrassing.

Thinking back to my initial prejudices, I cannot blame her. We ask patients intrusive, personal questions with the explicit guarantee of confidentiality, but also an implicit guarantee of freedom from judgment. Physicians, being human, are not immune from making presumptions about patients, whether intentional or not. We can be particularly unforgiving for diseases for which we blame the patient, ranging from obesity to depression to HIV. Rather than deny these thoughts exist, we should be cognizant of them and prevent them from affecting patient care. Mrs. Sen was so discouraged by this judgment that she delayed seeing a doctor until CMV had already consumed her eye. She hid out in her room, shedding pounds in parallel to her plummeting CD4 counts until she became so feeble and cachectic she wouldn't have been able to leave even if she wanted to. She was disappearing, both literally and figuratively. There have been such great strides in HIV research over the last thirty years that the virus itself no longer has to be a death sentence; however, the burden of shame it carries still makes it one.

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Lessons on Sickle Cell Disease

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One spring morning during my intern year of residency, I arrived on the medicine ward to discover that the overnight resident had admitted a patient in sickle cell crisis to my panel. This patient was only 27 years old, and had already suffered ten episodes of acute chest syndrome, three prior strokes, and avascular necrosis of the right hip. These complications had left her severely debilitated. She was now living in a permanent nursing home and would visit our hospital every couple of months for management of sickle cell crisis. The overnight resident had suggested that I spend as little time with the patient as possible. The resident had placed her on a Dilaudid patient-controlled analgesia (PCA) pump, and the patient seemed comfortable when alone. However, whenever the patient sensed someone else in the room she would immediately writhe in pain and push the Dilaudid pump for meds. Better to avoid her and not cause undue stress to the patient or the hospital staff, the resident advised.

I quietly slipped into my patient's room. She was asleep and was without a grimace on her eyebrow. In keeping with standard protocol for every patient on my service, I gently shook her awake to see how she fared through the night. Slowly, she opened her unfocused eyes as if coming out of a pleasant midsummer night's dream. When her gaze focused onto me she immediately released an agonizing scream and begged me to make the pain stop. She reached for her Dilaudid pump and quickly pressed it for relief. Moments later the patient's nurse rushed into the room and tried to shoo me away. Overnight, the nursing team had spent an inordinate amount of time trying to gain IV access for the patient's Dilaudid pump. Therefore the nurse wasn't going to allow me to lose the precious access off the patient's pinky finger because I didn't know what I was doing. When we were both outside the patient's room, the nurse quietly echoed what my overnight resident originally suggested: that the patient seemed to be in pain only when someone was near her. My patient, in the nurse's opinion, was a drug seeker.

During morning rounds, we reviewed my patient's chart. Her bloodwork was consistent with hemolysis, and she was very likely in an acute crisis. The attending suggested that my patient might also be suffering from a concomitant pain syndrome in which patients perceive legitimate pain, but experience that pain as something more intense than what they are actually feeling. Regardless, the plan remained the same: pain management, IV fluids, and supplemental oxygenation. If needed, we could insert a PICC line for more secure IV access. We then agreed upon the specific settings for my patient's Dilaudid pump, and I was instructed not to deviate from (i.e., increase) this setting.

During the first couple of days of my patient's admission, I made an effort to check on her as much as possible. Without fail, she would wince in pain and press her Dilaudid pump every time she saw me. But during those brief moments, she also shared snips and pieces of herself: her former life as a college student; her current life as a nursing home resident; her general loneliness as the only person under the age of 70 at her nursing home; her idea to educate medical students about the experiences of living with sickle cell disease because "they just don't get it;" her relationship with her father. I came to enjoy those moments together.

Then one day, she lost IV access during the middle of a pain crisis. The nurses didn't have to page me because I could hear her down the hall. My patient begged me not to attempt to place another IV line because it would hurt too much. I didn't listen to her. I also didn't regain access. Her oxygenation saturation was fine, but she was tachycardic. I asked her nurse to inject a hefty dose of Dilaudid. The nurse asked if that was advisable since the dose that I suggested was greater than what the patient would normally receive over the course of an hour on the Dilaudid pump. Because my patient's morning labs demonstrated hemolysis, and it was unlikely that she was faking tachycardia, I reasoned that she must be in true pain, and not just drug seeking or experiencing a pain syndrome. However, the injection didn't relieve her. My heart sank.

I placed an order for a PICC line. I had nothing left to offer to my patient, so I sat by her bedside. To this day I do not really understand what I was trying to achieve, nor do I know what I actually achieved, if anything. But for ten minutes I sat at my patient's bedside and bore witness to her pain. We sat together in silence. I offered no words. She volunteered no words. She never asked for more medication. She simply cried, and screamed, and moaned. I reached for her hand, and she allowed me to take it. The nurse would come in regularly, but she would quickly leave once she saw that I was with my patient. At one point during those ten minutes a member of the housekeeping staff entered the room and mopped the floor without acknowledging either one of us. I wondered how often this moment reflected my patient's reality: to cry out in excruciating pain, only to realize that everyone who walks by doesn't recognize that she even exists. I had never previously contemplated the possibility of such abject isolation.

I told my patient I needed to leave to coordinate the insertion of her PICC line. I left her room, with her pain ever ringing in my ears and mind. By the afternoon we had regained IV access with a PICC line and provided my patient with proper pain medication. By the end of that day, I thought I had learned something critical about sickle cell disease and crisis.

Specifically, I thought I learned that the key to effective pain management was not the proper selection of opioid medication, but the cultivation of a meaningful human connection. More than five months have passed since I discharged my patient. She has not yet been readmitted, and I imagine that she is still in the nursing home, alone and lonely, without a chance to return to her former life. As I reflect on it now, months later, I believe I have learned only one thing about the pain of sickle cell disease: I simply don't get it.

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Axillobifemoral Bypass Graft: A Student Dissection Experience

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As first-year medical students, we were excited, but nervous, to start the anatomy course. We were prepared to dedicate ourselves to the physical demands of dissection, and the hours of memorizing names and relations of countless anatomic features. We expected to leave the anatomy course with a comprehensive understanding of the human body that we would apply to our future studies and careers. We were not prepared, however, for the experience we had with our cadaver, Lucy.* Lucy was a small woman, but as we learned, she had endured a lot, physically and medically, in her 83 years of life. She had a pacemaker. She had coronary artery disease and a

triple bypass procedure. She also had severe peripheral artery disease and had undergone at least one extraordinary surgical graft procedure to maintain blood flow into her lower extremities. The surprise of discovering a small piece of an axillobifemoral bypass graft and then continuing to uncover it, region by region, throughout the anatomy course, brought our dissection experience and our connection to Lucy to a more profound level than we could ever have anticipated.

*The name Lucy was chosen as a pseudonym to protect the identity of the cadaver.

GETTING TO KNOW LUCY

We first met Lucy on a Wednesday evening the week prior to the start of the Clinical and Developmental Anatomy course. Our meeting was facilitated by a kind physician who volunteered to introduce us, and by our second-year peer assistant. Being in the anatomy lab for the first time, in the presence of so many deceased, was an overwhelming experience. Our physician carefully guided us through an inspection of Lucy's frail body. We identified several scars that hinted about procedures she had undergone, but otherwise Lucy seemed to be in pretty good shape.

DISSECTION REPORT

A week later, as we removed the skin from Lucy's thorax, we found a pacemaker resting on her left pectoralis major muscle. However, there was significant atrophy of her right pectoralis major muscle, which did not make much sense to us since the pacemaker was on her left side. Then, we uncovered a large, red, tube-shaped "muscle" running down the lateral aspect of her right chest. Truthfully, we didn't know what we had uncovered, but compared with other cadavers in the lab, we knew it was unusual and we were intrigued. Faculty members visited our cadaver to help us identify our "muscle." They were also unsure of what it was. Other students had hypotheses of their own. One thought it might be Lucy's esophagus. Another thought it might be a ventricular-peritoneal shunt.

By the time we left the thorax and moved on to Lucy's abdomen, we knew the "muscle" was a tube—a bypass graft—but we didn't know its origin or termination. Although we wanted to dissect the whole structure at once, we were instructed to follow the dissection sequence as dictated in

the course outline. As we progressed through each dissection module, we gradually uncovered the shunt.

During the abdomen dissection we found another surprise: The graft split into two components. The first continued straight down into Lucy's right thigh. The second arched across her lower abdomen toward her left thigh. Nevertheless, we could not follow the grafts.

As we reached the end of the abdomen dissection, we discovered that Lucy had an abdominal aortic aneurysm immediately proximal to the bifurcation of the aorta (Figure 1A, blue arrow). Inside the aorta was a large clot and the aortic walls were covered with plaque, as were the walls of the common iliac arteries. These indications of aortoiliac disease explained why the graft was designed to perfuse both limbs. At this point, one of the instructors from another lab visited our table and identified the tube as an axillobifemoral bypass graft (AXbiFBG). He briefly explained the procedure, and told us that he had rarely seen it in patients and had never seen one in a cadaver.

Throughout our dissection of Lucy, we identified evidence of vascular problems. In the thorax, a triple coronary bypass procedure had been performed and the heart was significantly enlarged. In the abdomen, in addition to the aortic aneurysm and plaque, we found a filter in the inferior vena cava (Figure 1A, green arrow). Despite evidence of severe vascular problems, Lucy's legs and feet appeared to be generally healthy and well-perfused, i.e. there was no ulceration or discoloration of the skin (Figure 1B). Thus, the AXbiFBG seemed to have successfully maintained Lucy's lower limb circulation.

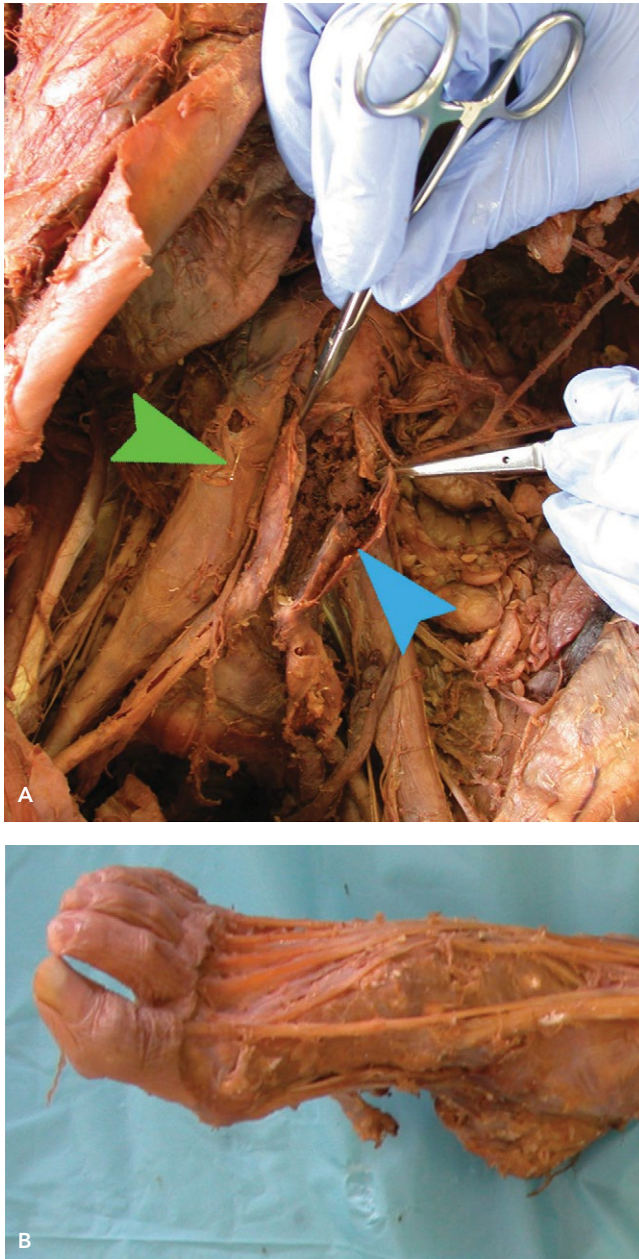


Figure 1 | A. Abdominal aortic aneurysm incised. Note the clot that extends bilaterally into the common iliac arteries (blue arrow). Inferior vena cava filter (green arrow). B. Right foot demonstrates no skin ulcers or discoloration indicating that there was adequate perfusion the limbs. Left foot was the same (not shown).

Before we could perform a detailed exploration of the proximal and distal portions of the graft, we had to complete dissection of the head and neck. In the meantime, we consulted the literature to find out more about AXbiFBG procedures. We learned that Lucy's graft was classified as an extra-anatomic bypass, in which the graft remains external to the body cavities in a tunnel created in the subcutaneous tissue. Extra-anatomic bypass procedures are indicated in elderly patients with significant limb ischemia, severe obstructive pulmonary disease, severe coronary artery dis-

ease, or chronic kidney disease (Mannick and Nabseth, 1968). Although we do not know when Lucy's graft was placed, we did find evidence of coronary artery disease as well as peripheral artery disease, perhaps explaining her candidacy for this extra-anatomic procedure.

We eagerly awaited the limb dissection modules so we could trace the remaining components of the graft.

By the time we reached the upper limb module, our dissection skills had improved significantly. Finally, we were able to follow the graft back to Lucy's right axillary artery, and demonstrate that some of the components of her medial brachial plexus were tangled around the proximal portion of the graft. According to Hoffman and Elliott (1987), in 62% of individuals the medial pectoral nerve (a branch of the medial cord of the brachial plexus) innervates the lower half or two-thirds of the pectoralis major muscle. Dissection of the pectoralis major and/or pectoralis minor muscle during the AXbiFBG procedure (Sauvage and Wood, 1966) may consequently injure the medial pectoral nerve. Although we did not trace it specifically, this was most likely the cause of atrophy of the costal portion of Lucy's right pectoralis major muscle.

During the lower limb dissection, we traced the graft into both of Lucy's femoral arteries. The vertical portion of the graft (Figure 2A) extended from her right axillary artery (Figure 2B) down to her right femoral artery. The horizontal portion of the graft extended from the right femoral graft, across her abdomen just superior to the pubic bone, to her left femoral artery (Figure 2C). At last we had uncovered the entire graft, and concluded a very satisfying experience. Our ability to at last observe the graft in its entirety made us all the more curious about the history and details of the AXbiFBG, and motivated us to research and compose a brief historical review that is included in this issue of the journal (Mishall et al., 2016)

CONCLUDING REMARKS

Words cannot fully describe the impact that human cadaver dissection has on a student. Each day in the anatomy lab we made new discoveries about Lucy, and gained insight into the life of a person suffering from coronary and peripheral artery disease. In addition to learning a tremendous amount about the human body and several clinical procedures, we came to understand a great deal about ourselves through this process. With the help of our cadaver-patient, Lucy, we grew as individuals and as team members. Over the four-month anatomy course, every member of our team became attached to Lucy, and our last day with her was an emotional one. Unfortunately, we will never know all the details about her interesting medical history, but we sincerely hope that the AXbiFBG improved her quality of life and contributed to her happiness. We are very grateful to her and will forever be thankful for her courageous gift.

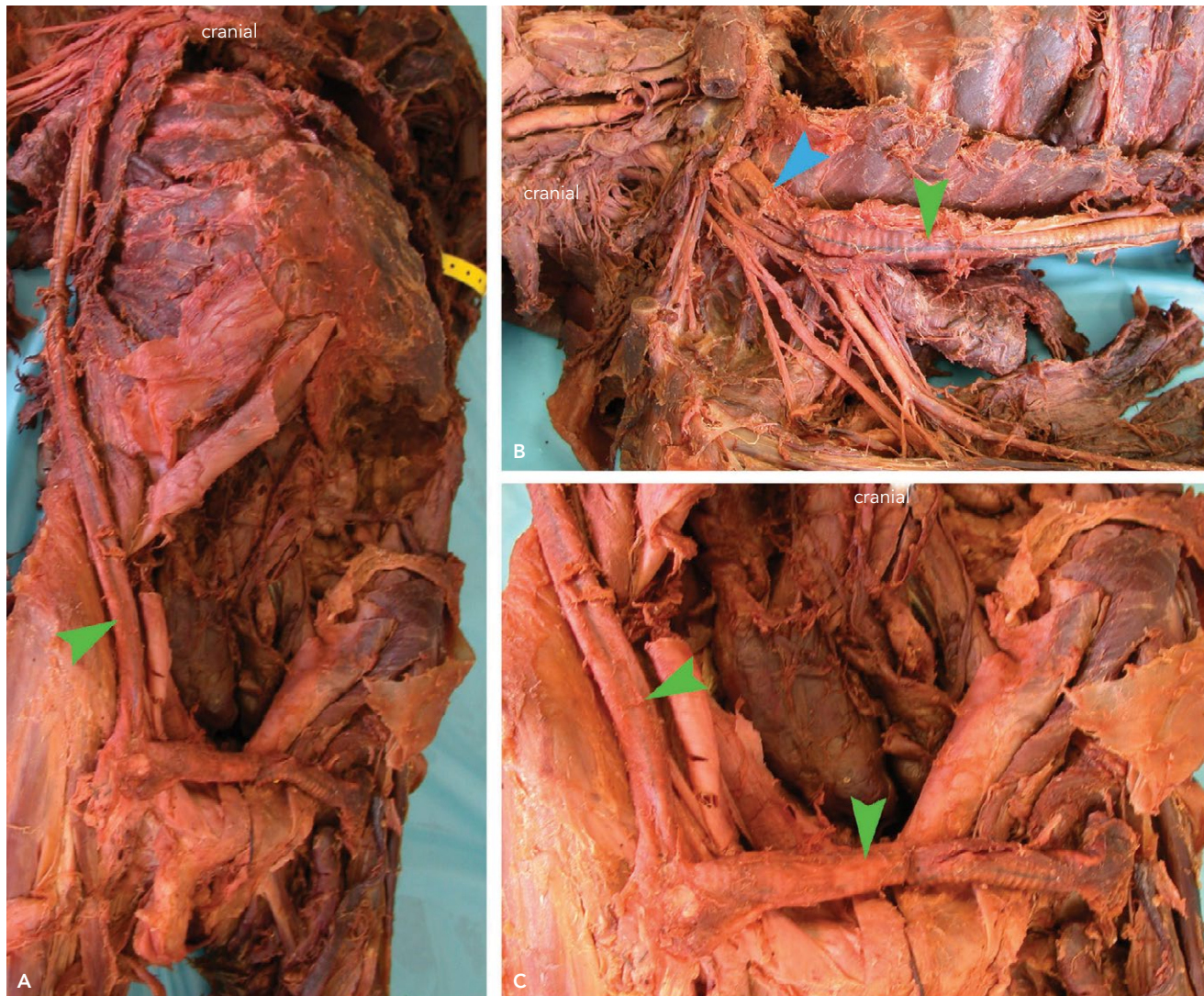


Figure 2 | Axillobifemoral bypass graft (Dacron®) in a cadaver-patient. A. Entire axillobifemoral graft *in situ*. B. Close up of the axillary graft. The axillofemoral graft (green arrows) originated in the right axillary artery (blue arrow) and tunneled between the pectoralis major muscle and thoracic wall. C. Close up of the bifemoral graft.

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Autophagy and Schizophrenia: A Closer Look at How Dysregulation of Neuronal Cell Homeostasis Influences the Pathogenesis of Schizophrenia

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Autophagy, the process of degrading intracellular components in lysosomes, plays an important role in the central nervous system by contributing to neuronal homeostasis. Autophagic failure has been linked to neurologic dysfunction and a variety of neurodegenerative diseases. Recent investigation has revealed a novel role for autophagy in the context of mental illness, namely in schizophrenia. This article summarizes the phenomenology, genetics, and structural/histopathological brain abnormalities associated with schizophrenia. We review studies that demonstrate for the first time a connection between autophagy malfunction and schizophrenia. Transcriptional profiling in schizophrenia patients uncovered a dysregulation of

autophagy-related genes spatially confined to a specific area of the cortex, Brodmann Area 22, which has been previously implicated in the positive symptoms of schizophrenia. We also discuss the role of autophagy activators in schizophrenia and whether they may be useful adjuncts to the traditional antipsychotic medications currently used as the standard of care. In summary, the field has progressed beyond the basic concept that autophagy impairment predisposes to neurodegeneration, to a mechanistic understanding that loss of autophagy can disrupt neuronal cell biology and predispose to mood disorders, psychotic symptoms, and behavioral change.

INTRODUCTION

Neurons, like all cells, must achieve a delicate balance between synthesis and degradation of proteins to maintain a healthy existence. The complex machinery that regulates protein homeostasis is an example of how cells maintain a necessary equilibrium to comply with spatial limitations and functional need. Continuous surveillance of the intracellular environment is accomplished by the combined action of the chaperone network (a conglomerate of proteins that aids in protein folding and assembly) and protein degradation pathways (microsystems that degrade proteins and recycle their constituent amino acids). These mechanisms ensure that misfolded proteins and damaged organelles can be rapidly identified and eliminated. Failure to perform this quality control leads to accumulation of damaged products that are toxic for cells and can precipitate loss of cellular functionality and even cell death (Morimoto & Cuervo, 2009).

Protein degradation pathways are essential for preserving neuronal health, functionality, and homeostasis. Autophagy—a term that means “self-eating”—is one such protein degradation pathway that functions to degrade a diverse array of cellular components in vesicular organelles called lysosomes (Figure 1). Lysosomes contain a collection of more than 60 acid hydrolases capable of cleaving and digesting most biological material (Schroder, Wrocklage, Hasilik, & Saftig, 2010). After digestion, breakdown products are shipped back into the cytosolic compartment by transporters embedded in the lysosomal membrane.

Autophagy is a complex process because it involves the sensing, sequestering, and targeting of cargo (i.e., damaged organelles and misfolded proteins). Different mechanisms of cargo delivery to lysosomes exist, including *de novo* formation of cargo-containing autophagosomal vesicles that fuse with lysosomes (in macroautophagy), receptor-mediated translocation of cytosolic proteins across the lysosomal membrane (in chaperone-mediated autophagy), and invagination and pinching off of portions of the lysosomal membrane (in microautophagy) (Yang & Klionsky, 2010). More than 30 autophagy-related genes (ATGs) and their protein products have been identified to participate in these various steps of autophagy. These include molecules involved in signal transduction (e.g., PI3K, BECN1), autophagosome formation and elongation (e.g. ATG5, ATG12, ATG16), and lipid conjugation (e.g. LC3, ATG3) (Mizushima, Yoshimori, & Ohsumi, 2011). In addition to the genes that comprise the core autophagic machinery, there are other regulatory proteins that serve to modulate autophagy activity either through activation or inhibition. These include genes such as *ULK2*, which has been shown to be necessary for proper autophagy induction in mammals (Mizushima, 2010); *BCL2*, which inhibits Beclin1-dependent autophagy (Pattingre et al., 2005); and *ADNP*, which encodes a binding partner of LC3, a critical component of the autophagosome (Gozes & Ivashko-Pachima, 2015). Regardless of the mechanism or genes that are involved, a major role of autophagy is to identify and eliminate potentially toxic materials before they accumulate inside post-mitotic neurons and lead to dysfunction and death. Additionally, autophagy has been shown to

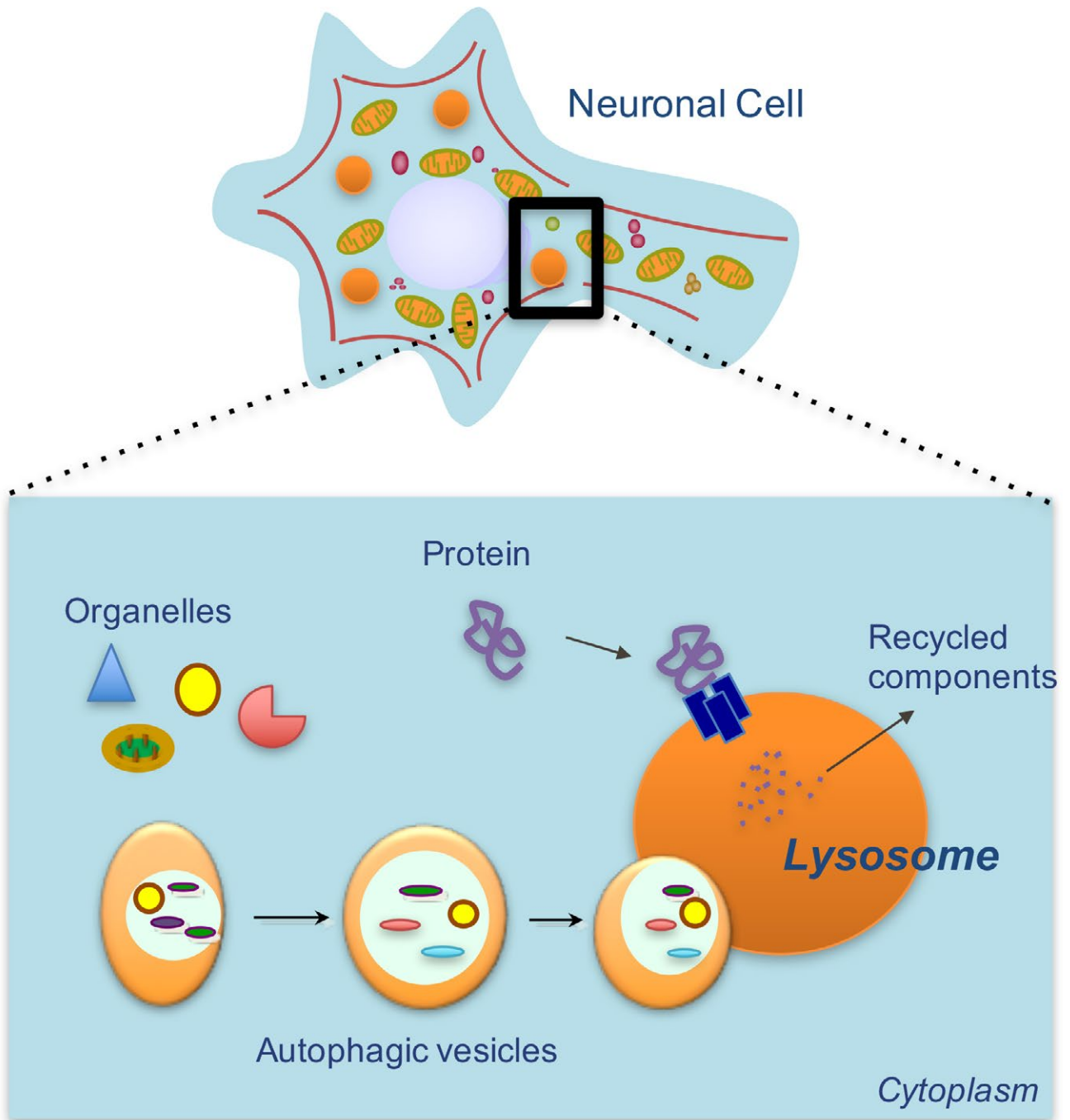


Figure 1 | Autophagy in Neuronal Cells. The process of autophagy refers to the intracellular degradation of proteins and organelles inside lysosomes. The broken-down material is subsequently recycled by release back into the cytoplasm. Autophagy helps to maintain neuronal homeostasis by degrading damaged proteins and dysfunctional organelles that could otherwise result in cellular toxicity and death.

have several other important functions in neurons, such as recycling of basic metabolites for new synthesis and energy stores, facilitating the adaptive stress response, contributing to development, and regulating synaptic plasticity (Nixon, 2013; Nikolettou, Papandreou, & Tavernarakis, 2015).

Autophagic failure has been linked to neurologic dysfunction and a variety of neurodegenerative diseases (Nixon & Yang, 2012; Schneider & Cuervo, 2013). Studies have shown that blockage of the autophagy pathway in neurons leads to cell death and early-onset neurodegeneration in rodent models (Hara et al., 2006). Moreover, there is strong evidence demonstrating that dysfunctional autophagy is associated with disorders such as Alzheimer's disease (J.-H. Lee et al., 2010), Parkinson's disease (Orenstein et al., 2013), Huntington's disease (Ravikumar et al., 2004), and tauopathies (Wang, Martinez-Vicente, et al., 2009).

In addition to its role in neurodegeneration, autophagy is now being investigated in the context of psychiatric illness. Studies from the past five years have illustrated a potentially important connection between autophagic dysfunction and schizophrenia, a mental illness that affects approximately one percent of the world's population and causes debilitating social and occupational impairment. Diagnostic criteria for schizophrenia include the presence of two or more *positive symptoms*—such as hallucinations and delusions—or *negative symptoms*—such as blunted emotional responsiveness, poverty of speech, and amotivation (*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5), 2013). Positive symptoms represent an exaggeration of normal processes that result in a distortion of reality, often manifested as auditory hallucinations and paranoid delusions. Disorganized speech and behavior are also hallmarks of schizophrenia and encompass findings such as tangential speech, derailment, neologisms, and incoherence. Negative symptoms, on the other hand, are conceptualized as an absence or diminution of normal processes, or deficit symptoms. Patients with negative symptoms may exhibit blunted or flattened affect, alogia, avolition, and anhedonia (Andreasen & Olsen, 1982).

THE BASIS OF SCHIZOPHRENIA: GENETIC, ENVIRONMENTAL, PATHOLOGICAL AND MOLECULAR ASPECTS

From our current understanding of the illness, schizophrenia is likely the result of complex interactions between genetic and environmental factors that predispose to abnormalities in the central nervous system. Schizophrenia is believed to have a strong genetic component given that family, twin concordance, and adoption studies have all demonstrated a high degree of heritability. The concordance rate has been reported to be as high as 40 to 50% in monozygotic twins and 10 to 15% in dizygotic twins (Kringlen, 2000). Recent genome-wide association studies (GWAS) have identified 22 risk loci and thousands of genetic changes (single-nucleotide polymorphisms, SNPs) that could contribute to one's risk (Ripke et al., 2013). While the increased concordance among monozygotic twins suggests a strong genetic component, the fact that the concordance rate doesn't reach

100% suggests that there are additional environmental factors that influence one's risk for developing schizophrenia.

Although there seems to be a genetic component to the etiology of schizophrenia, it appears that there is no single gene solely responsible for causing the disease. However, emerging evidence suggests that environmental influences may have a significant contribution. These factors include perinatal complications, drug use, and traumatic brain injury. Various obstetrical difficulties such as hemorrhage, preterm labor, maternal-fetal blood group incompatibility, and fetal hypoxia may increase the risk of developing schizophrenia by up to two-fold (Clarke, Harley, & Cannon, 2006). There is evidence that maternal infections (especially TORCH infections such as toxoplasmosis), as well as other pregnancy-related complications such as nutritional deficiencies, allergies, and maternal stress may predispose to schizophrenia (Svrakic, Zorumski, Svrakic, Zwir, & Cloninger, 2013). Epidemiological studies have revealed that certain illicit drugs, namely cannabis, increase one's risk (van Os et al., 2002), as does suffering from an early traumatic brain injury, specifically if it leads to frontal and temporal lobe damage (Nicholl & LaFrance, 2009).

In addition to understanding the biological and environmental predisposing factors, there is clinical interest in deciphering structural and histopathological abnormalities of the brain that are associated with schizophrenia. Experts believe that different brain regions play distinct roles in positive and negative symptomatology, an idea that is supported by the observation that antipsychotic agents that antagonize dopamine receptors alleviate positive symptoms (J. Lee et al., 2015). For instance, blockage of dopamine (D2) receptors in the auditory and auditory-visual association cortices (Brodmann Areas 22, 39, 42, 20, and 37) is one proposed mechanism for a reduction in hallucinatory behavior in schizophrenia (Goldsmith, Shapiro, & Joyce, 1997). Nonetheless, global changes in the brain have been identified and linked to schizophrenia, such as the bilateral enlargement of ventricles that reflects an underlying loss of tissue in the central nervous system (Styner et al., 2005). Postmortem brain neuropathology in schizophrenia has revealed synaptic and dendritic deficits in the cerebral cortex and hippocampus (Benes, Kwok, Vincent, & Todtenkopf, 1998). These findings on pathology have been correlated with neuroimaging evidence that shows reduced grey matter volume and a 40% reduction in volume in the CA2 region of the hippocampus (Glantz, Gilmore, Lieberman, & Jarskog, 2006). Furthermore, a particular area of the prefrontal cortex, Brodmann Area 10 (BA10), has been reported to have functional connectivity impairment in patients with schizophrenia, which is believed to correlate with deficits in memory (Wang, Cui, et al., 2009).

While there have been numerous studies exploring the genetic, environmental, and pathological aspects of the illness, the molecular basis of schizophrenia is still poorly understood. To appreciate the molecular underpinnings of schizophrenia, investigators have started examining the changes in gene expression associated with schizophrenia and how these alterations in neuronal cell biology may

underlie positive and negative symptoms (Narayan et al., 2008). Excitingly, global gene expression studies have identified changes in transcriptional regulation of genes related to myelination, synaptic transmission, metabolism, and, most recently, autophagy (Barnes et al., 2011). Therefore, it is reasonable to hypothesize that failure of autophagy in neurons may lead to cellular dysfunction and global changes in distinct brain regions that contribute to the development of symptoms of schizophrenia.

THE FIRST STUDIES LINKING AUTOPHAGY TO SCHIZOPHRENIA

Large-scale, high-throughput analyses were the first tests of choice to help uncover molecular changes that are associated with schizophrenia. To determine whether schizophrenia is accompanied by alterations in gene expression in certain regions of the brain, investigators compared gene expression profiles across multiple brain areas of postmortem patients who fell into either of two groups: those who were cognitively normal (no neuro- or psychopathology), and those who had been diagnosed with schizophrenia (Horesh, Katsel, Haroutunian, & Domany, 2011). Strikingly, this unbiased analysis revealed a gross impairment in autophagy-related gene expression in brains from schizophrenia patients, particularly in Brodmann Area 22 (BA22) of the superior temporal cortex, a region already hypothesized to be involved in the pathogenesis of schizophrenia (Horesh et al., 2011; Rapoport et al., 1999). The molecular signatures that demonstrated the highest significance ($p=0.00039$), differentiating affected brains from control specimens, were a cluster of genes involved in the regulation of autophagy. Microarray analysis of these brains showed that several genes that are key in neuronal autophagic function exhibited decreased expression levels in the BA22 region. The list included genes like *ULK2*, *ATG3*, and *PI3KR4*, which are involved in different facets of macroautophagy (regulation, signaling, autophagosome formation and lipid modification, respectively) (Kroemer, Mariño, & Levine, 2010). Thus, this study concluded that patients who had been diagnosed with schizophrenia during their lifetimes exhibited a decrease in mRNA expression of several autophagy-related genes, suggesting for the first time a molecular link between schizophrenia and autophagic dysfunction.

A second group performed a similar transcriptional analysis of mRNA expression levels in postmortem samples from 19 control patients and 23 schizophrenia patients. This study compared two different brain regions thought to be involved in the positive and negative symptoms of schizophrenia (Barnes et al., 2011). Gene expression was analyzed in the BA22 region, which is hypothesized to play a role in the development of the positive symptoms of schizophrenia. Similarly, genetic profiling was done on the anterior prefrontal cortex (BA10), which is thought to contribute to the negative symptoms of schizophrenia. Interestingly, the results demonstrated that autophagic dysregulation was a prominent feature only in the BA22 region, but not the BA10 region, thus reaffirming the concept that autophagy dysregulation occurs in the brain region associated with

positive symptoms (Barnes et al., 2011). The authors proposed that autophagy failure is more highly associated with positive symptom pathophysiology due to the spatial dysregulation of autophagy gene expression in specific brain regions of patients diagnosed with schizophrenia.

After these transcriptional profiling studies established a connection between schizophrenia and autophagic gene dysregulation, the question became: *Does autophagy failure contribute to the pathogenesis of schizophrenia and, if so, how?*

AUTOPHAGY AND SCHIZOPHRENIA: UNDERSTANDING THE MECHANISM

A recently published landmark study by Merenlender-Wagner et al. proposed a mechanism for neuronal dysregulation in schizophrenia that is due to autophagy (Merenlender-Wagner et al., 2015). This group showed that there is a statistically significant reduction in mRNA levels of a crucial autophagy-related protein, Beclin 1 (BECN1), in the hippocampus of schizophrenia patients. A BECN1-interacting protein, BCL2, was also found to have altered transcript levels in the postmortem hippocampal region of these same patients. Since BECN1 plays a critical role in autophagy induction, a decrease in its expression may result in impairment of autophagy in hippocampal neuronal cells, thus limiting their capacity to degrade damaged components inside the cellular milieu (Merenlender-Wagner et al., 2015).

In contrast to the decrease in BECN1 in schizophrenia patients, another autophagy-related protein called activity-dependent neuroprotective protein (ADNP) exhibits increased levels in both the brain and circulating lymphocytes in schizophrenia. ADNP is a binding partner of LC3, a key component of the autophagic machinery. Merlender-Wagner and colleagues postulated that disturbance of ADNP in schizophrenia has a negative effect on autophagic activity via LC3. Interestingly, ADNP levels are also altered outside of the brain and in peripheral blood, suggesting that this protein may serve as a biomarker for certain types of psychiatric illness (Merenlender-Wagner et al., 2015).

Administration of NAP, a peptide fragment of ADNP also known as davunetide, enhanced the ADNP-LC3 interaction and reversed the decrease in hippocampal *BECN1* mRNA levels in a mouse model of schizophrenia (MAP6-deficiency) (Merenlender-Wagner et al., 2014). Normalization of *BECN1* expression by NAP led to positive outcomes in the behavioral phenotype of MAP6-deficient mice. The changes observed in treated animals included decreased hyper-locomotion and cognitive deficits as measured by the object recognition test. The combination of NAP with clozapine, an FDA-approved antipsychotic used in refractory schizophrenia, resulted in complete normalization of behavioral outcomes (Merenlender-Wagner et al., 2014). These studies highlight a potential role for NAP-mediated autophagy rescue in mouse models of schizophrenia and suggest a new therapeutic strategy of supplying adjuvant treatment along with antipsychotic medication to bolster the efficacy of therapy.

AUTOPHAGY AND ANTIPSYCHOTICS

Medications used to treat a variety of psychiatric illnesses may function in part through induction of autophagy. Previous studies demonstrated that the mood-stabilizing drug lithium, used to treat bipolar disorder, induces autophagy (Sarkar & Rubinsztein, 2008). This finding prompted others to evaluate whether antipsychotic agents have an effect on autophagy activity in the brain. Zhang and colleagues used a small molecule screen to show that three FDA-approved antipsychotic agents (fluspirilene, trifluoperazine, and pimozide) are all inducers of autophagy (Zhang et al., 2007). This suggests that downregulation of autophagic genes in certain brain regions of schizophrenia patients might be reversed, at least in part, by antipsychotic drugs that drive autophagy activity and enhance the expression of autophagy-related proteins in the BA22 region.

However, the relationship between autophagy and antipsychotic medication is not entirely clear. Conflicting studies in rat primary neurons have demonstrated that certain typical and atypical antipsychotics (haloperidol and clozapine) actually block autophagy activity by inhibiting the formation of autophagolysosomes, a key intermediate compartment necessary for lysosomal degradation of intracellular cargo (Park et al., 2012). This study also showed that these medications decrease neuronal viability through autophagic inhibition. Therefore, the effect of antipsychotic medication on autophagy may depend on the type of drug, the region of the brain affected, and other unknown confounding variables. In any case, it will be important to test whether certain antipsychotic medications act via autophagy, how this occurs, and whether adding therapeutic agents that modulate autophagic activity can enhance the efficacy of the medications currently used as the standard of care.

CONCLUSION

The cellular process of autophagy may be an important contributor to the pathophysiology of psychiatric disease, namely schizophrenia. While previous studies have established that the failure of autophagy predisposes to neurodegeneration and dementia, recent findings have linked autophagy to neuropsychiatric disease and have helped to elucidate potential underlying molecular mechanisms in schizophrenia. The traditional view was that autophagic compromise leads to protein misfolding and subsequent aggregation, which in turn drives neuronal cell death and early dementia. Now, we are beginning to understand that loss of autophagy may also disrupt neuronal cell biology in a way that predisposes to mood disorders, psychotic symptoms, and behavioral change (Polajnar & Zerovnik, 2014).

Going forward, additional research is needed to establish whether functional changes in autophagic activity occurs in schizophrenia patients. Until now, the studies linking autophagy to psychiatric disease have mainly focused on genetic profiling and steady-state levels of the genes and proteins involved in autophagy. Future areas of research will need to explore the mechanisms by which autophagy is actually impaired and whether this loss of function contributes to positive or negative symptoms, or to both.

Furthermore, GWAS studies can be performed to evaluate whether SNPs in autophagy-related genes may predispose to the development of schizophrenia, thus providing a novel explanation for inherited schizophrenia. Importantly, we still cannot distinguish whether autophagy failure predisposes to schizophrenia, or whether other molecular changes characteristic of schizophrenia result in compromised autophagy. Teasing out whether autophagy impairment is a cause or a consequence of schizophrenia necessitates further studies using mammalian models of this disease.

In addition to the behavioral symptoms that are currently used to fulfill the diagnostic criteria of schizophrenia, future studies of autophagy and psychiatric illness may aid in the development of biomarkers that correlate with disease progression, severity, and responsiveness to treatment. Perhaps the contribution of autophagy to schizophrenia pathophysiology only occurs in a subset of patients; therefore biomarkers would be useful to identify which patients have an autophagic defect. If future studies continue to demonstrate a causative effect of autophagic malfunction on schizophrenia, small-molecule autophagy activators that cross the blood-brain barrier may serve as a useful adjunctive therapeutic tool. Further investigation may support the implementation of autophagy activators in conjunction with other FDA-approved antipsychotic medications to target schizophrenia symptoms more effectively.

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The following abstracts received the Marmur Research Prize at the 20th annual Julius Marmur Symposium.

VITAL ROLES OF KINESINS IN DEVELOPMENT AND DISEASE IN ZEBRAFISH

Philip D. Campbell. Mentor: Dr. Florence L. Marlow

Kinesin-1, a dimer of Kif5 proteins, was the first Kinesin motor discovered and has been implicated in numerous biological processes. Invertebrates possess a single *kif5* gene, but mammals have three *kif5* genes, *kif5A*, *kif5B*, and *kif5C*, which may support diversification of Kinesin-1-mediated biological processes. Due to their similar protein structures and functions *in vitro*, Kif5s are thought to act largely redundantly. However, *kif5* mouse knock-outs have distinct phenotypes and human mutations in *kif5A* and *kif5C* cause distinct diseases. To study how the expanded vertebrate *kif5* family contributes to development and disease, I utilized molecular genetic approaches in the zebrafish vertebrate genetic system. Using *kif5B* zebrafish mutants that I generated and available *kif5A* mutants I have identified cell-type specific roles for individual *kif5s*. Specifically, loss of *kif5A* causes a sensory-motor syndrome in zebrafish reminiscent of *kif5A* loss in humans. I have shown that Kif5A transports mitochondria to the periphery of sensory axons and prevents axonal degeneration. Furthermore, overexpression of Kif5A but not of other Kif5s prevents sensory neuropathy. My analysis of *kif5B* revealed its requirement in the egg to properly pattern the embryonic axes and to specify the germline stem cells. I have shown that perturbed patterning results from cytoskeletal and cargo localization defects in the zygote. Altogether, my work demonstrates that Kif5s play important roles in both development and disease and that while individual Kif5s share some functions, some Kif5s uniquely fulfill cell-type specific functions.

HOW THE BRAIN HANDLES SENSORY UNCERTAINTY

Fanny Cazettes. Mentor: Dr. Jose L. Pena

Imagine hearing the siren of an ambulance while driving a car. If loud enough, it is possible to tell where the ambulance is coming from, and pull over accordingly. However, if music is playing on the radio or passengers in the car are talking, locating the direction of the siren with certainty becomes challenging. To handle the uncertainty associated with noisy and ambiguous sensory stimuli, our brain must evaluate how reliable sensory information is at any given time. However, the strategy that the brain uses to decide the appropriate behavior from noisy information is debated. We addressed this question in the sound localization system of the owl, combining neural recordings, behavioral measurements and computational modeling. We found that neurons in the owl's brain are a priori selective to the information that is most reliable, and able to capture the degree to which this information can be trusted on a moment-by-moment basis. In light of these results, we then asked how the activity of these neurons is used to guide the owl's orienting behavior when uncertainty varies. To do so, we recorded the neurons that command the owl's characteristic head-turn toward sounds. We found that these neurons integrate information such that their output signals commanding the owl's orienting behavior capture the direction of the source weighted by the uncertainty in the sensory cues. Therefore, our work sheds light on the code used by the brain to capture sensory uncertainty and command behavior efficiently.

OPTICAL TOOLS TO STUDY THE ISOFORM-SPECIFIC ROLES OF SMALL GTPASES IN IMMUNE CELLS

Veronika Miskolci. Mentor: Dr. Dianne Cox & Dr. Louis Hodgson

Despite the 92% homology between Rac1 and Rac2, these isoforms play non-redundant roles in hematopoietic cells. To study the isoform-specific dynamics of Rac isoforms in live cells, we optimized and developed isoform-specific, genetically-encoded, single-chain FRET-based biosensors for Rac1 and Rac2, respectively. In addition, we employed several strategies, including selective promoter usage and our recently reported "synonymous modification" to achieve stable, full-length expression of biosensor in hematopoietic cells, critical for proper biosensor readout and data interpretation. We functionally validated these biosensors in a murine monocyte-macrophage subline of RAW 264.7 cells in the context of forming actin-rich protrusions. Rac1 and Rac2 had similar activation kinetics yet distinct spatial distributions in response to fMLP; active Rac1 localized to the cell periphery while active Rac2 broadly localized in the perinuclear region. Morphodynamic analysis of Rac1, Rac2 and Cdc42 activities during the extension of random protrusions revealed that Rac2 played a leading role in the generation of random protrusions; Rac2 strongly activated first in regions distal from the leading edge, followed by the activation of Rac1, Rac2 and Cdc42 immediately behind the leading edge. Overall, partnering the use of optimized, isoform-specific biosensors should be valuable for interrogating the coordination of Rho GTPase activities in living cells.

NEUTROPHIL AGING IS REGULATED BY THE MICROBIOME

Dachuan Zhang. Mentor: Dr. Paul S. Frenette

Blood polymorphonuclear neutrophils provide immune protection against pathogens but also may promote tissue injury in inflammatory diseases. Although neutrophils are generally considered as a relatively homogeneous population, evidence for heterogeneity is emerging. Under steady-state conditions, neutrophil heterogeneity may arise from ageing and the replenishment by newly released neutrophils from the bone marrow. Aged neutrophils up-regulate CXCR4, a receptor allowing their clearance in the bone marrow, with feedback inhibition of neutrophil production via the IL17/G-CSF axis, and rhythmic modulation of the haematopoietic stem cell niche. The aged subset also expresses low levels of L-selectin (CD62L). Previous studies have suggested that *in vitro*-aged neutrophils exhibit impaired migration and reduced pro-inflammatory properties. Here, we show using *in vivo* ageing analyses that the neutrophil pro-inflammatory activity correlates positively with their ageing in the circulation. Aged neutrophils represent an overly active subset exhibiting enhanced M2 integrin (Mac-1) activation and neutrophil extracellular trap (NET) formation under inflammatory conditions. Neutrophil ageing is driven by the microbiota via Toll-like receptors (TLRs)- and myeloid differentiation factor 88 (Myd88)-mediated signaling pathways. Depletion of the microbiota significantly reduces the number of circulating aged neutrophils and dramatically improves the pathogenesis and inflammation-related organ damage in models of sickle cell disease or endotoxin-induced septic shock. These results thus identify an unprecedented role for the microbiota in regulating a disease-promoting neutrophil subset.

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