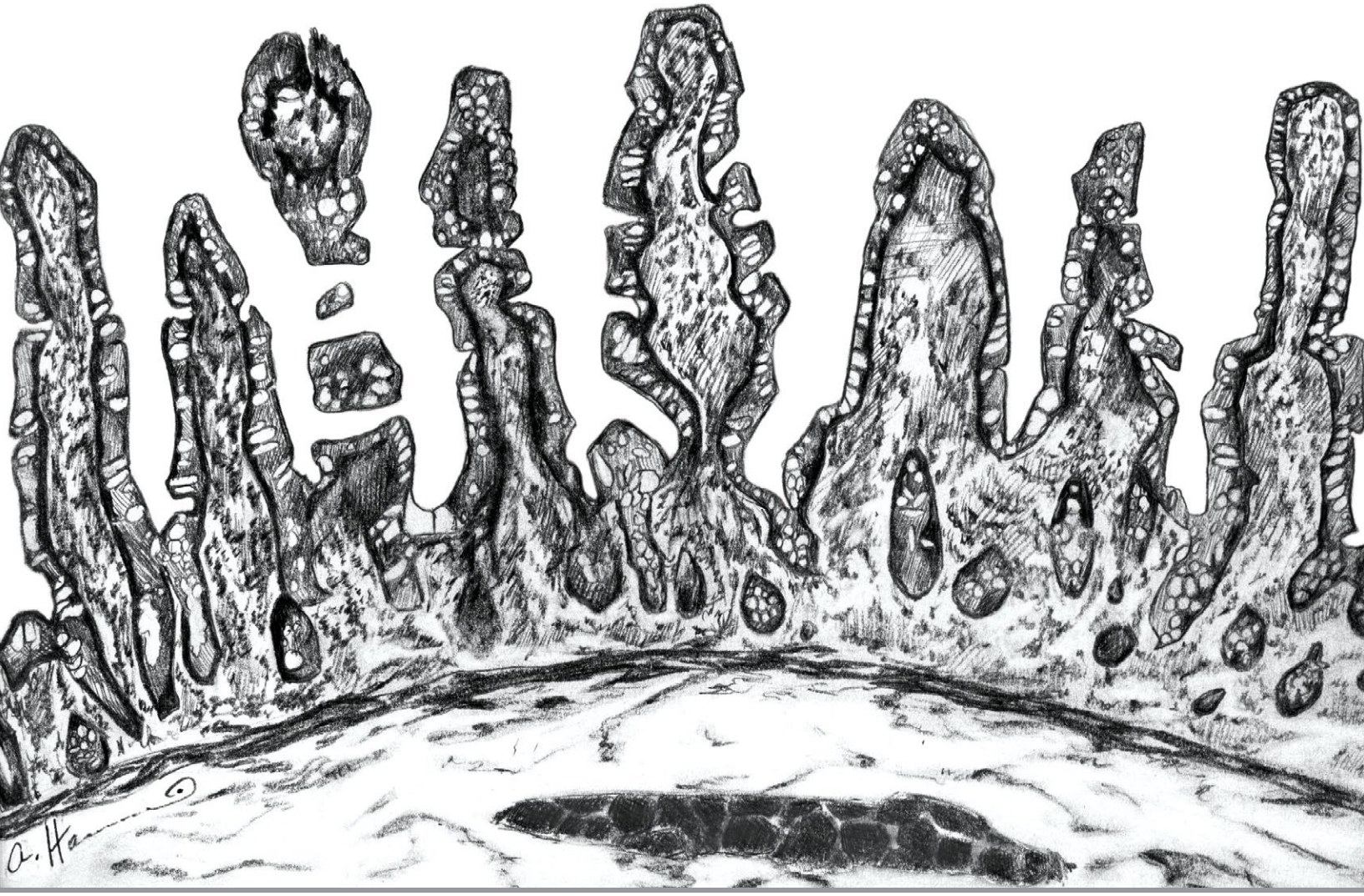
EJBM

THE EINSTEIN JOURNAL
OF BIOLOGY AND MEDICINE
Volume 29, Issues 1 & 2, 2013



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SCOPE AND PURPOSE

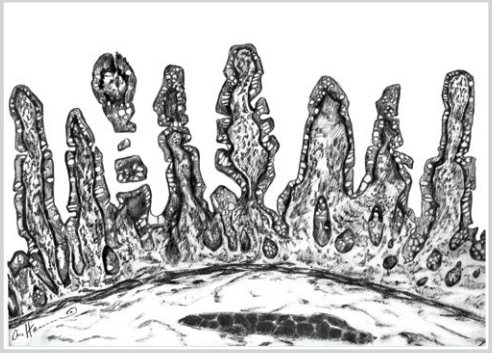
The *Einstein Journal of Biology and Medicine (EJBM)* is a peer-reviewed general medical scientific journal edited by the students, faculty, and alumni of Albert Einstein College of Medicine. The major purpose of *EJBM* is to serve as a forum for the basic and clinical investigation being conducted by the members and alumni of Albert Einstein College of Medicine as well as other academic medical scientific institutions. In addition, an important aim of *EJBM* is the publication of articles written by students, postdoctoral fellows, house officers, and junior faculty members. Thus, *EJBM* encourages original investigation by scientists and physicians in training.

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.

EJBM publishes two issues per year and is funded through grants from the Office of Medical Education at Albert Einstein College of Medicine. For more information or to submit a manuscript, please visit our website **(http://www.einstein.yu.edu/ejbm).** Contact us at: **ejbm@med.einstein.yu.edu**.

The Editorial Board would like to thank Frances and Robert Kramer and Kathie Kramer Rudy for their generous gift in support of *The Einstein Journal of Biology and Medicine*.
 ISSN: 1559-5501. Printed in the United States on acid-free paper.

Inside This Issue



EJBM Cover Art
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Editor-in-Chief
Michael Shusterman

Inside This Issue

Announcing the new EJBM Weblog

Read exclusive online only commentary on biomedical and clinical topics on the *EJBM Weblog* at

theejbm.wordpress.com.
Learn more about how you can become a contributor online.

This issue is dedicated to the memories of Dr. Richard M. Hays and Dr. Sharon Silbiger.

Perceptions of an Implantable Cardioverter-Defibrillator: A Qualitative Study of Families with a History of Sudden, Life-Threatening Cardiac Events, and Recommendations to Improve Care

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Objective: To identify major concerns associated with implantable cardioverter-defibrillators (ICDs) and to provide recommendations to adult and pediatric physicians involved in the care of patients with ICDs.

Background: Cardiac ion channelopathies are a well-recognized cause of sudden cardiac death in infants, children, adolescents, and young adults. ICDs are effective in preventing sudden death from fatal arrhythmias in patients with known cardiac channelopathies. There is a paucity of research on the effect of ICDs on quality of life in patients with cardiac channelopathy diagnoses, especially young patients.

Methods: A qualitative study interviewing patients and families affected by inherited arrhythmias was conducted. Fifty participants with personal or family histories of cardiac events or sudden death were interviewed individually or in focus groups by clinical psychologists. All interviews were transcribed verbatim and then analyzed and coded based on current qualitative research theory to identify themes related to the research question. Twenty-four participants discussed ICDs in their interviews.

Results: Participants reported concerns about ICDs, and these concerns were categorized into six themes: (1) comprehension and physician-patient communication; (2) anxiety; (3) restrictions and fallacies; (4) complications; (5) utility; and (6) alternative therapy. Participants noted communication breakdowns between providers and their colleagues, and between providers and their patients. Participants and their families experienced many different forms of anxiety, including worry about the aesthetics of the ICDs and fears of being shocked. Multiple restrictions, fallacies, and complications were also cited.

Conclusion: Interview themes were used to formulate recommendations for counseling and educating patients with ICDs.

INTRODUCTION

Ventricular tachyarrhythmias are the most common cause of sudden cardiac death (SCD). Among ventricular tachyarrhythmias, primary and secondary ventricular fibrillation represent the major causes of SCD (Bayés de Luna, Coumel, & Leclercq, 1989). Cardiopulmonary resuscitation may preserve brain function and prevent end organ damage temporarily; however, the only effective treatment for ventricular fibrillation is prompt electrical defibrillation. Implantable cardioverter-defibrillators (ICDs) are more effective than anti-arrhythmic agents for the secondary prevention of SCD, especially after a previous life-threatening cardiac event. ("A Comparison of Antiarrhythmic-Drug Therapy," 1997; Akhtar et al., 1993; Connolly et al., 2000; Kuck, Cappato, Siebels, & Rüppel, 2000). Evidence has supported the use of ICDs as a treatment modality for secondary prevention in patients with a history of ventricular tachycardia, ventricular fibrillation, or successful resuscitation from SCD, and for primary prevention in patients at severe risk for developing ventricular tachycardia, ventricular fibrillation, or both (Epstein et al., 2008).

Significant causes of ventricular tachycardia and ventricular fibrillation are the congenital cardiac channelopathies, including long QT syndrome (LQTS), Brugada syndrome (BS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and short QT syndrome (SQTS). Cardiac channelopathies, inherited in an autosomal dominant pattern with variable penetrance, present with a range of phenotypes. Channelopathies are potentially lethal, with reports of 6% to 13% of individuals with LQTS experiencing cardiac arrest or SCD before the age of 40 if not treated (Modell & Lehmann, 2006). Many patients are asymptomatic until their initial clinical manifestation of sudden death. In addition, 25% of patients with LQTS have "concealed" phenotypes in which they are at risk for cardiac arrhythmias but do not have prolonged QT intervals on electrocardiograms (Goldenberg et al., 2011). Cardiac channelopathies produce ventricular tachyarrhythmias via the abnormal conduction of ions through affected ion channels responsible

for depolarizing and repolarizing the cardiac myocyte cell membrane, resulting in abnormal electrical conductance throughout the heart. These channel abnormalities are inherited as gain-of-function or loss-of-function mutations in families, placing first-degree relatives of affected individuals at considerable risk of inheriting the same genetic mutations. Therefore, genetic testing has emerged as a useful screening tool for identifying cardiac channelopathies in patients and their families with a strong clinical suspicion of this diagnosis (Boussy et al., 2010).

Evidence suggests that LQTS, BS, CPVT, and SQTS are significant causes of SIDS and SUDS (Arnestad et al., 2007; Tester & Ackerman, 2009). Sudden infant death syndrome (SIDS) is defined as the sudden death of a child under the age of 12 months with no identifiable medical cause after a thorough investigation. Sudden unexplained death syndrome (SUDS) refers to the unexplained death of a person between the ages of 1 and 25, 30, 35, or 40 (depending upon the source). Sudden unexplained death in childhood (SUDC) applies to the sudden death of a child between the ages of 1 and 18. Therapy for cardiac channelopathies often involves primary and secondary prevention of ventricular tachyarrhythmias through the implantation of ICDs, along with beta blocker therapy and lifestyle modification (Kaufman, 2009).

Complication rates related to ICDs have been reported at approximately 30%. Surgical complications, generator-related problems, lead complications, and inappropriate shocks have been identified as the most common complications (Alter, Waldhans, Plachta, Moosdorf, & Grimm, 2005). Similar complications have been identified in the pediatric population, with the addition of a significant psychosocial impact on patients' lives (Shah, 2009).

There is a paucity of research investigating the effect of ICDs on the quality of life of patients with cardiac channelopathy diagnoses, especially young patients. As part of a larger qualitative study of patients and families primarily affected by inherited arrhythmias to investigate the ethical and social issues associated with genetic testing, we performed a secondary analysis on the impact of ICDs. In their comments, participants often spontaneously raised issues related to ICDs. A secondary analysis of the data identified themes associated with ICDs. This study identifies important topics for healthcare providers to discuss with their patients living with or considering ICD placement.

METHODS

Recruitment of Families

This study is an analysis of comments voiced by a subset (24 out of 50) of the subjects enrolled in the Montefiore Einstein Center for CardioGenetics' study on the ethical issues raised by the translation of genetic knowledge into clinical practice. The subjects were chosen for the subset if they spontaneously mentioned ICDs in their interviews or focus groups. The original study focused on evaluating and organizing ethical, legal, and social issues associated with cardiogenetic diseases linked to potentially fatal cardiac arrhythmias (Barlevy et al., 2012; Cohen et al, 2012). Fifty participants were interviewed individually or in focus groups to learn about their subjective experience of having a cardiogenetic disease. Associated ethical and social issues were evaluated. All participants in the study had histories, either personal or family, of cardiac events with clinical diagnoses of cardiac arrhythmia, or of relatives who had died from SIDS or SUDS.

The study population was recruited from three different sources: patients being cared for at the Montefiore Einstein Center for CardioGenetics (n = 27); respondents to an invitation posted in a newsletter from the Sudden Unexplained Death in Childhood Program (n = 9); and respondents to an invitation posted in a newsletter from the Sudden Arrhythmia Death Syndromes Foundation (n = 14). Prior to study participation, each recruited individual provided written informed consent and completed a questionnaire containing demographic information. The study protocol was reviewed and approved by the Institutional Review Board of Albert Einstein College of Medicine/Montefiore Medical Center.

Interviews and Transcription

All interviews and focus groups were conducted by clinical psychologists either in person or over the telephone. Open-ended questions were used to promote discussion about participants' experiences with cardiac arrhythmias or sudden death. Focus groups were composed of two or more unrelated individuals. Interviews were conducted with individuals and family units. All interviews and focus groups were recorded with audio devices and were subsequently transcribed verbatim. Transcripts were de-identified to protect participants' privacy. For the present study, comments were identified and extracted that were specifically relevant to the participants' experiences with ICDs.

Coding and Analysis of Transcripts

The transcripts from this study as well as the parent study were analyzed by the grounded theory approach developed by Auerbach and Silverstein (2003). This approach groups regularly used words and phrases from different interviews or focus groups into repeating ideas, and then groups these similar repeating ideas into themes, further describing the research question.

Statistical Analysis

A chi-square test was performed comparing the subjects included in the ICD study to the subjects excluded from the study.

RESULTS AND DISCUSSION

Participant Population and Demographics

Demographic information for the entire population and the participants who discussed ICDs is provided in Table 1. Thirty-nine women and 11 men participated in the overall study, and 21 women and three men discussed ICDs.

Table 1 | Demographic Characteristics of All Participants

Characteristics	Total Number of Participants	Participants Who Discussed ICDs	Participants Who Did Not Discuss ICDs	χ^2 p-value for ICD Study v. Excluded
	(*n* = 50)	(*n* = 24)	(*n* = 26)	
Sex				p = 0.119
Male	11 (22.0%)	3 (12.5%)	8 (30.8%)	
Female	39 (78.0%)	21 (87.5%)	18 (69.2%)	
Age				p = 0.698
< 20	1 (2.0%)	0 (0.0%)	1 (3.8%)	
21–30	9 (18.0%)	6 (25.0%)	3 (11.5%)	
31–40	9 (18.0%)	3 (12.5%)	6 (23.1%)	
41–50	14 (28.0%)	7 (29.2%)	7 (26.9%)	
51–60	11 (22.0%)	5 (20.8%)	6 (23.1%)	
> 60	6 (12.0%)	3 (12.5%)	3 (11.5%)	
Race				p = 0.560
African American	7 (14.0%)	3 (12.5%)	4 (15.4%)	
White	42 (84.0%)	20 (83.3%)	22 (84.6%)	
Asian	1 (2.0%)	1 (4.2%)	0 (0.0%)	
Ethnicity				p = 0.396
Latino/Hispanic	10 (20.0%)	6 (25.0%)	4 (15.4%)	
Non-Latino/Hispanic	40 (80.0%)	18 (75.0%)	22 (84.6%)	
Education				p = 0.166
Less than Ninth Grade	1 (2.0%)	1 (4.2%)	0 (0.0%)	
GED	2 (4.0%)	2 (8.3%)	0 (0.0%)	
High School	5 (10.0%)	4 (16.7%)	1 (3.8%)	
Some College	12 (24.0%)	4 (16.7%)	8 (30.8%)	
College Degree	12 (24.0%)	6 (25.0%)	6 (23.1%)	
Graduate Degree	15 (30.0%)	7 (28.0%)	8 (30.8%)	
Unknown	3 (6.0%)	0 (0.0%)	3 (11.5%)	
Marital Status				p = 0.139
Married	27 (54.0%)	15 (62.5%)	12 (46.2%)	
Cohabiting	2 (4.0%)	0 (0.0%)	2 (7.7%)	
Separated	2 (4.0%)	2 (8.3%)	0 (0.0%)	
Divorced	1 (2.0%)	0 (0.0%)	1 (3.8%)	
Widowed	3 (6.0%)	0 (0.0%)	3 (11.5%)	
Single	15 (30.0%)	7 (29.2%)	8 (30.8%)	
Annual Household Income				p = 0.032
< $25,000	6 (12.0%)	4 (16.7%)	2 (7.7%)	
$26,000–$50,000	6 (12.0%)	5 (20.8%)	1 (3.8%)	
$51,000–$80,000	10 (20.0%)	7 (29.2%)	3 (11.5%)	
> $80,000	21 (42.0%)	7 (29.2%)	14 (53.8%)	
Refused	2 (4.0%)	1 (4.2%)	1 (3.8%)	
Unknown	5 (10.0%)	0 (0.0%)	5 (19.2%)	

A chi-square analysis was performed comparing ICD discussants and nondiscussants, and the populations were found to be similar. Among those who discussed ICDs, two participants had diagnoses of Brugada syndrome, 19 participants had diagnoses of long QT syndrome, two participants had diagnoses of short QT syndrome, and one participant did not have a diagnosis. Of these participants, 10 had undergone ICD implantation, while 14 had not. Among those participants who had not elected to have ICDs placed, 42% were parents of children with ICDs and were intricately involved in the decision-making process (Table 2).

Table 2 | ICD Study Participant Diagnoses and Presence/Absence of ICDs

Characteristics		Number of Participants (n = 24)
Diagnosis*		
BS		2 (8.3%)
LQTS		19 (79.2%)
SQTS		2 (8.3%)
Unknown		1 (4.2%)
ICD		
Yes		10 (41.7%)
No		14 (58.3%)
	Child with ICD	6 (42.9%)
	No Child with ICD	8 (57.1%)

*Patient diagnoses are listed: Brugada syndrome (BS), long QT syndrome (LQTS), short QT syndrome (SQTS), and unknown diagnoses. Presence or absence of an internal cardioverter-defibrillator (ICD) is listed for the participants. Participants without ICDs but with children who have ICDs are also listed.

Identified Themes

Multiple themes were identified during the discussion. Themes identified include comprehension and physician-patient communication, anxiety, complications, restrictions and fallacies, utility, and alternative therapy (Table 3 - 5).

Many ICDs were implanted in participants during or after emergency situations in which the participants had experienced life-threatening arrhythmias. During these circumstances, participants often expressed fear of the emergency surgery and noted that they were unsure of what was happening:

> "The last thing I remember is turning on the TV to watch a movie. . . . I woke up, EMS was there. . . . I didn't know what was going on and [the doctors] told me I had to have the pacemaker placed. I was really scared." Female, age 29

The gravity of the situation often required urgent, rapid device implantation. Participants and their family members were often frightened and had difficulty comprehending the situation:

> "[F]irst thing I remember hearing from the doctor was they had to put a defibrillator/pacemaker. . . . You gotta explain to me . . . talk to me in plain English. . . . I'm thinking my daughter is dying here." Female, age 51

Furthermore, participants and family members often did not completely understand the cardiac channelopathies and their treatments. Many participants used the terms "ICD" and "pacemaker" interchangeably and could not provide a clear distinction between the two:

> "When [the doctor] explained it to me, in my mind [I thought], 'My 7-year-old needs a pacemaker?' I mean defibrillator, pacemaker—in my mind it's the same thing. Only 80-year-olds need that, not my 7-year-old." Female, age 29

Another issue raised by participants involved communication with medical staff. Many participants expressed dissatisfaction when asking hospital staff to listen and comply with their decisions. One member of a family who was well known to the hospital staff due to the previous loss of a child from SUDS commented:

> "My daughter ran into a tree [while driving] and doesn't remember [the accident]. . . . [The paramedics] told us to go to the emergency room and get an EKG. . . . The doctors recognized me and our name . . . one simple EKG turned into an overnight stay in the ICU. . . . [The cardiologist] was going to put in a defibrillator right then and there and I said, 'No! We have an electrophysiologist.'" Female, age 46

Another woman described an encounter with medical staff regarding her ICD and her prior experiences with inappropriate shocks:

> "I got to the hospital. . . . I told [the staff] that I have this device and my heart is not slowing down. And [the nurse told me] to breathe. And I told her it's not working. It's going to shock me. . . . As soon as I saw the [heart-rate monitor] get up to 170, 176 hit. I braced myself . . . and it shocked me. . . . They have medication that slows down your heart!" Female, age 30

Some participants described miscommunication between patients and medical staff, while others described communication breakdowns among providers within the medical community:

> "[The doctors] felt that R had Brugada syndrome and the only way to prevent another event was to put in an ICD. . . . [The doctors] said we need to go ahead and not wait for the genetic test to come back, he needs an ICD. . . . [Years later] the neurology department . . . determined that [my son] actually had a seizure. . . .

> Electrocardiologists [now] think there is nothing wrong with R's heart; it was a misdiagnosis. I wish they would have slowed down. . . . We didn't know; as parents we were scared to death." Female, age 58

Another participant reported further perceived dissension:

> "Originally, [the physicians] were suggesting a pacemaker. . . . [O]nce [the genetic testing] came back negative, [the physicians] were pretty much writing [my disease] off." Female, age 25

Despite some examples of communication breakdown between physicians and their colleagues as well as physicians and their patients, effective physician-patient interactions led to improved medical knowledge and insight into other participants' diseases:

> "[The doctors] placed the defibrillator . . . [as a] safety measure; were my heart to stop, [the ICD] would activate, give me a jump start and give me an opportunity to live through [the arrhythmia]." Female, age 55

> "I have LQT1, which is more benign. . . . If I had [LQT subtype] 2, 3, or 4 [the doctors] would really insist that I get the ICD." Female, age 34

Patients who sought second and third opinions concerning their diagnoses, and received consistent recommendations from cardiologists as well as geneticists, appeared to have a better understanding of their disease and appeared more satisfied with the treatment, which in many cases was to receive an ICD:

> "I got about three different doctors' opinions. I saw the genetic group. . . . [The physicians agreed] I should go [get the ICD placed]. . . . I'm looking at all my options and I said, 'Just get it, you never know, might save your life.'" Female, age 52

> "[M]y QT interval was around 600. . . . It was very much a long QT syndrome. . . . I went through several doctors . . . . they all said I should get the ICD." Female, age 24

Contemplating receiving and living with ICDs caused multiple types of anxiety in participants. Proband anxiety refers to those fears experienced primarily by the patient who had the ICD or was contemplating receiving an ICD himself or herself. Caregiver anxiety describes fears specific to parenting, with the caregiver having a heritable channelopathy himself or herself, or having an affected child. Finally, relative/friend anxiety represents the concerns of those close to an affected proband.

After being diagnosed with familial cardiac channelopathies, participants often considered having ICDs placed. One of the most common anxiety-producing thoughts was the concept of having a foreign device inside one's body forever. To many, this was an extremely scary thought with a constant reminder:

> "[The ICD] feels weird. Once in a while when you feel the bump, and you know that's not actually supposed to be there." Female, age 52

> "The ICD to me was really scary. I thought of cutting my body open and putting this titanium box in [my body] . . . seemed so freaky and alien to me." Female, age 34

Table 3 | Comprehension and Physician-Patient Communication Theme Identified and Described with Examples

Theme	Description	Example
Comprehension and Physician-Patient Communication	Emergency Situation	• "[F]irst thing I remember hearing from the doctor was they had to put a defibrillator/pacemaker. . . .You gotta explain to me . . . talk to me in plain English. . . . I'm thinking my daughter is dying here." Female, age 51
	ICD Definition	• "When [the doctor] explained it to me, in my mind [I thought], 'My 7-year-old needs a pacemaker?' I mean defibrillator, pacemaker—in my mind it's the same thing. Only 80-year-olds need that, not my 7 year-old." Female, age 29
	Communication Breakdown	• "Originally, [the physicians] were suggesting a pacemaker. . . . [O] nce [the genetic testing] came back negative, [the physicians] were pretty much writing [my disease] off." Female, age 25
	Improved Patient Insight	• "[The doctors] placed the defibrillator . . . [as a] safety measure; were my heart to stop, [the ICD] would activate, give me a jump start and give me an opportunity to live through [the arrhythmia]." Female, age 55
	Multiple Physician Opinions	• "I got about three different doctors' opinions. I saw the genetic group . . . [The physicians agreed] I should go [get the ICD placed]. . . . I'm looking at all my options and I said, 'Just get it, you never know, might save your life.'" Female, age 52

Table 4 | Anxiety Themes Identified and Described with Examples

Anxiety Theme*	Description	Example
Proband	Foreign Device	• "The ICD to me was really scary. I thought of cutting my body open and putting this titanium box in [my body] . . . seemed so freaky and alien to me." Female, age 34
	Aesthetics	• "I am a small person. [My ICD] is very pronounced. A friend of mine wanted to see it after I had the surgery. I said, 'Just don't gasp.' I showed her and [my friend] was like, 'ahhhh. . . .' 'I told you not to gasp!'" Female, age 46
	Shocks	• "ICDs have killed people misfiring and having an event from your ICD. . . . I was feeling so scared and nervous." Female, age 46
Caregiver	Dependence	• "I do most of the parenting. . . . [W]hat if something happened to me and I had this little 3-year-old?" Female, age 46
	Change of Opinion with Family	• "I had just had kids and I started thinking, 'If I have short QT, then I want to be able to be around as long as I can for my children.'" Female, age 25
	Witnessed Event	• "[S]he went on a vacation with the family, and the defibrillator went off twice. . . . All she could remember was seeing her kids scream. . . . [W]hat got her more afraid were the two little guys there watching her go through this." Female, age 52
	Affected Child	• "[My daughter] is very active . . . always bouncing. How do I say to her, 'I'm afraid you might die'?" Female, age 29
Friend/Relative	Support System	• "She gets scared her device is gonna go off, so I'll go over there, but I'm scared. When she sleeps, she shakes. I'm constantly making sure she's okay or waking her up. I'm scared sometimes to be with her by myself." Female, age unknown

* The anxiety themes are categorized into three subgroups: Proband (participant is affected by cardiac channelopathy), Caregiver (participant is affected with children or unaffected with an affected child), Friend/Relative (other participants are unaffected by the disease).

Another anxiety-provoking thought for participants involved the aesthetic effects of ICD placement. Many participants expressed extreme emotional concern over body disfigurement as a result of implantation:

> "It was told to [my wife and me] that if she did have a pacemaker this definitely would have saved her. . . . She was very petite and she didn't want one because the doctor was saying that it would be visible." Male, age 31

Many participants' own insecurities with their devices were further reinforced by the thoughts of others:

> "I am a small person. [My ICD] is very pronounced. A friend of mine wanted to see it after I had the surgery. I said, 'Just don't gasp.' I showed her and [my friend] was like, 'ahhhh . . . ' 'I told you not to gasp!'" Female, age 46

Although many participants were unhappy with the size and appearance of the ICD in their chest, some expressed enthusiasm that devices are becoming smaller over time:

> "When did you have the ICD put in?" "Two years ago and then before that it was seven years. They put a whole new one in because the other one was big and stuck out. This [ICD] is nice. You can't even tell I have it, other than the scar. The other one was ugly." Female, age 51

After the ICDs were implanted, many participants were terrified of the potential shocks from the devices. They expressed concern about what it would feel like, what they would be doing should the devices go off, and whether or not help would be nearby:

> "Do you worry about the shocks?" "At first I did. You don't really know what's gonna set it off. [The doctors] can try to prepare you, but until it happens you have the anxiety, 'Is it gonna come?'" Female, age 52

> "ICDs have killed people misfiring and having an event from your ICD . . . I was feeling so scared and nervous." Female, age 46

Finally, related to a fear of being shocked, participants expressed anxiety about being alone if their devices fired:

> "I called [my mother]. It makes me feel comfortable that somebody knows where I am. Because if I passed out, [my mother] already knows where I am and she could do something about it. I call my mom. I call my sisters. I'll call anyone." Female, age 29

Having a family was an extremely influential factor in decid-

ing to have an ICD implanted. Participants were often uninterested in the ICD for themselves; however, they often wanted ICDs to be able to save their lives for the sake of their spouses and children:

> "I didn't really want to [have the ICD placed]. . . . My husband made me feel for him I should, for [my kids and grandkids] I should, but for me, I am not afraid of the long QT." Female, age 51

> "I do most of the parenting. . . . [W]hat if something happened to me and I had this little 3-year-old?" Female, age 46

Opinions of participants tended to change when they were considering becoming parents. When contemplating starting a family, participants who had never considered having ICDs expressed changes in their perspective:

> "I was born this way. I am 34 years old. I am still alive; if [long QT syndrome] takes me out of this world, this is nature unfolding. . . . If I have a child [my views] may change because then someone else's life is dependent on me." Female, age 34

Another participant expressed similar views after years of not following up with a cardiologist regarding her diagnosis of short QT syndrome:

> "I had just had kids and I started thinking, 'If I have short QT, then I want to be able to be around as long as I can for my children.'" Female, age 25

Not only are children extremely important in the decision about ICD implantation, they also often represented a source of anxiety for patients in whom ICDs had been placed. Participants voiced concerns regarding family members, especially children, witnessing a syncopal episode followed by appropriate defibrillation:

> "[S]he went on a vacation with the family, and the defibrillator went off twice. . . . All she could remember was seeing her kids scream. . . . [W]hat got her more afraid were the two little guys there watching her go through this." Female, age 30

Table 5 | Complications, Restrictions, and Rumors, and Utility Themes Identified and Described with Examples

Theme	Description	Example
Restrictions & Rumors	MRI Restrictions	• "R had an MRI, which was his one and only, and now he will never have an MRI [again] because the leads will be in his body forever. I think most people think a seizure is a seizure when it actually could be the heart. It is very rarely reversed." Female, age 58
	Cell Phone Function	• "My mom has a defibrillator. . . . [S]he's restricted [from] using her cell phone in her left hand. Do you have restrictions like that?" "I do my best to use my right hand . . . but since I'm a lefty, I [try not to] touch the defibrillator." Female, age 38
	External Defibrillator	• "External defibrillators make people very nervous. Parents of my daughter's friends are not comfortable being alone [with my daughter]. . . . [My daughter's] school started giving us trouble. [The school] was not rejecting kids with asthma inhalers or Epipens. Why are they rejecting a child with an external defibrillator?" Female, age 46
Complications	Multiple Surgeries	• "[My son will] have a new defibrillator this June. The battery is failing and the epicardial system—he's outgrown it. . . . It starts the whole thing again—anesthesia, what if we lose him? It'll be like that for the rest of his life." Female, age 35
	ICD Storm	• "I got shocked 15 times in a row, inappropriately! It is a miracle my heart doesn't have scars or damage because of this machine. . . . Getting shocked by [an ICD] is worse than childbirth. I'd rather give birth to a thousand babies, than be shocked one time by [an ICD]." Female, age 30
Utility	Satisfaction	• "Are you glad you got the defibrillator?" "[I]f it ever saves my life, I'll say 'Yes.' Considering it's never had to shock me yet, I can't say 'Yes' and I can't say 'No.'" Female, age 38
Alternative Therapy	Meditation	• "I had some friends who do deep meditation [who suggested I meditate] to feel better about my choice [not to have an ICD]. I visualized a ball of white light that will come and wrap around my heart and protect it. . . . I would do that daily. . . . I still do it from time to time . . . [H]ey, it's been eight years [and no events]." Female, age 34

Parents voiced concerns when their children were affected by channelopathies and had defibrillators. Sources of anxiety in this situation included guilt and the question of communicating with children. Caregivers expressed guilt about passing the disease on to their children, and many participants discussed the desire to undergo genetic testing for family-planning purposes. Additionally, parents described feelings of anxiety that events might occur and they would not be present to take care of their children. Explaining to children why they needed ICDs was often difficult. Parents were anxious about affected children running, jumping, and playing competitive sports, and even explaining to their children the reasons for their anxiety was worrisome to many:

> "[My daughter] is very active . . . always bouncing. How do I say to her, 'I'm afraid you might die'?" Female, age 29

Below is an example of an effective communication strategy that one participant used to explain the disease to her daughter:

> "[My daughter] doesn't view [ICD placement] as major surgery. I told her, 'Your heart takes a little bit longer to restart than most people. [The doctors] want to give you an [ICD] so that if something happens, you'll be okay until someone can get you to the doctor.'" Female, age 29

Much of the focus on anxiety has been on that felt by patients and parents, but it is important to remember that cardiac channelopathies affect the entire family. Many participants expressed having strong support systems in their families and many of these close relatives and family friends expressed anxiety as well:

> "She gets scared her device is gonna go off, so I'll go over there, but I'm scared. When she sleeps, she shakes. I'm constantly making sure she's okay or waking her up. I'm scared sometimes to be with her by myself." Female, age unknown

Receiving ICDs was a life-changing experience for participants. Not only did the participants undergo surgery and live with the worry of arrhythmogenic events and device firing, but they were no longer able to participate in many activities that they had previously. Participants described restrictions on their regular exercise habits, which was emotionally difficult for many. They also talked about being unable to go through metal detectors or obtain MRI scans. The inability to have an MRI scan affected one participant who was misdiagnosed with Brugada syndrome and is now believed to have a seizure disorder:

> "R had an MRI, which was his one and only, and now he will never have an MRI [again] because the leads will be in his body forever. I think most people think a seizure is a seizure when it actually could be the heart. It is very rarely reversed." Female, age 58

Participants also described a notion that others do not and cannot fully understand the implications of living with ICDs. Participants' quality of life changed, and many individuals had to modify their lifestyles and plan to be close to medical facilities at all times in the event that arrhythmias requiring ICD firing should occur.

Some participants expressed beliefs concerning ICDs that are not necessarily true. One patient often expressed fear that using a cell phone would prevent his device from working properly:

> "My mom has a defibrillator. . . . [S]he's restricted [from] using her cell phone in her left hand. Do you have restrictions like that?" "I do my best to use my right hand . . . but since I'm a lefty, I [try not to] touch the defibrillator." Female, age 38

Restrictions associated with external defibrillators were also expressed. External defibrillators are widely prescribed for patients with cardiac channelopathies. They provide a means for quick defibrillation during sudden cardiac arrhythmias, and often serve to empower parents and family members close to patients who may otherwise feel powerless to help those afflicted. However, one participant expressed restrictions regarding play dates and school attendance because of her daughter's external defibrillator:

> "External defibrillators make people very nervous. Parents of my daughter's friends are not comfortable being alone [with my daughter]. . . . [My daughter's] school started giving us trouble. [The school] was not rejecting kids with asthma inhalers or Epipens. Why are they rejecting a child with an external defibrillator?" Female, age 46

Many participants mentioned ICDs in the context of complications they experienced secondary to ICD implantation. Complications described included a serious infection that required device explantation, and a fractured device lead shortly after initial surgical implantation requiring explantation with a second device implantation. Many participants described problems with battery life and the need for multiple surgeries every five to seven years. Participants expressed concern over recurrent surgeries, and regardless of the number of procedures required, they commented that it never got easier:

> "[My son will] have a new defibrillator this June. The battery is failing and the epicardial system—he's outgrown it. . . . It starts the whole thing again—anesthesia, what if we lose him? It'll be like that for the rest of his life." Female, age 35

One participant suffered from frequent inappropriate shocks and experienced an "ICD storm" with perpetuating, continuous shocks secondary to an initial inappropriate device firing:

> "I got shocked 15 times in a row, inappropriately! It is a miracle my heart doesn't have scars or damage because of this machine. . . . Getting shocked by [an ICD] is worse than childbirth. I'd rather give birth to a thousand babies, than be shocked one time by [an ICD]." Female, age 30

Because of the lifestyle restrictions and complications associated with ICD placement, many participants reported dissatisfaction with the devices. Most commonly their disappointment was with device utility, meaning that during the time when many patients had their devices implanted, they never required an appropriate defibrillation shock. Although this could be considered positive, given the invasiveness of the initial and subsequent procedures and the implications for quality of life, patients were at times ambivalent about their decision to have ICDs implanted:

> "Are you glad you got the defibrillator?" "[I]f it ever saves my life, I'll say 'Yes.' Considering it's never had to shock me yet, I can't say 'Yes' and I can't say 'No.'" Female, age 38

One participant found meditation extremely helpful in reducing the anxiety surrounding her heart condition, especially given her decision not to undergo device implantation.

> "I had some friends who do deep meditation [who suggested I meditate] to feel better about my choice [not to have an ICD]. I visualized a ball of white light that will come and wrap around my heart and protect it. . . . I would do that daily. . . . I still do it from time to time. . . . [H]ey, it's been eight years [and no events]." Female, age 34

CONCLUSION

Participants in this study reported recurrent issues when discussing ICDs, including comprehension and physician-patient communication, anxiety, complications, restrictions and fallacies, utility, and alternative therapy. These results were similar to many of the findings in the current literature examining the quality-of-life implications of ICD implantation (Eckert & Jones, 2002; Kamphuis, de Leeuw, Derksen, Hauer, & Winnubst, 2003; Syska et al., 2010; Wójcicka, Lewandowski, Smolis-Bak, & Szwed, 2008).

Our findings include many that are consistent with those of previous studies. A qualitative study by Anderson and colleagues focusing on the impact of living with a diagnosis of LQTS identified several important themes, including concern for family members, limitations in their daily lives, and a lack of understanding within a medical community fraught with uncertainty, misinformation, and inaccurate advice regarding clinical management (Andersen, Øyen, Bjorvatn, & Gjengedal, 2008).

The psychological ramifications of living with ICDs have been studied, representing the heart-disease population at large. Patients with severe heart disease who require ICD implantation often suffer from co-morbid depression. In patients affected by co-morbid depression at implantation, depression persists in 72% of patients post-implantation. Patients with clinical depression and ICDs are at increased risk of shocks (36%) compared with nondepressed patients (9%) (Suzuki et al., 2010). In a longitudinal study following patients with ICDs over four years, mental-health scores and overall psychological health scores improved significantly, while overall quality-of-life scores remained stable after device implantation (Carroll & Hamilton, 2008). Two studies identified younger age at implantation as a significant risk factor for the development of clinical depression and anxiety as well as worsening quality of life (Friedmann et al., 2006; Thomas et al., 2006). A recent study by Probst and colleagues found that patients diagnosed with Brugada syndrome reported that ICDs have a negative social impact on their lives (Probst et al., 2011).

One study examining physicians' views of their patients' quality of life post-implantation found that 47% of patients reported the same quality of life and 15% reported worsening quality of life with significant emotional and relationship strain. Furthermore, physicians reported discomfort in providing emotional and psychological support to their ICD patients, indicating the need for improved communication and encouragement from providers caring for patients with ICDs (Sears et al., 2000). In a randomized trial evaluating the use of ICD patient education and cognitive behavioral therapy, patients were less anxious, had lower cortisol levels, and reported increased acceptance of their ICDs after the intervention, further supporting the need for improved physician-patient communication in patients with ICDs (Sears et al., 2007).

Our study identified communication breakdown as a major cause of distress among patients receiving ICDs. Communication issues were not addressed in the published literature. Patients expressed their desire to have the opportunity to discuss ICDs prior to implantation, and in cases where this did not occur, more complications and dissatisfaction resulted. If immediate implantation was required, family members, especially caregivers, desired that they be informed about the reasons for device implantation and allowed to voice their concerns to ease anxiety, especially during emergency situations. This suggests that the need for an ICD, the mechanism of action of the ICD, and all risks and benefits of the procedure should be addressed prior to implantation, if possible. It is important not only to be effective communicators, but to be effective listeners as well. Although some patients were uneducated regarding their illness, others were extremely well informed. Patients and families were capable of comprehending these illnesses when provided with the appropriate tools, and their wishes should be respected as long as the patients or the healthcare proxies provided appropriate justification for decisions.

Many participants were ambivalent about their ICDs. Although the ICDs had been placed to protect them

Table 6 | Summary of Suggestions

Suggestions	Description
Promote Communication	• Providers should encourage their patients to speak with cardiologists and geneticists or genetic counselors to further understand their disease. • Providers should use open communication strategies to elicit concerns from patients with cardiac channelopathies and ICDs. • Providers should elicit common misconceptions from patients, and empower patients with knowledge addressing these fallacies. • Providers should encourage communication concerning family planning when appropriate. • Providers should encourage open communication among family and friends. A strong support system is important for patients with cardiac channelopathies.
Encourage Anxiety-Alleviating Strategies	• Patients may find deep meditation and other strategies helpful in controlling their anxiety. • These strategies may be used as adjunct therapies in conjunction with current treatment guidelines.
Provide Information on ICD Support Groups	• Support groups will likely ease the potential sense of isolation, and may provide insight and offer strategies to combat the anxiety-provoking factors concerning the patients' disease and their ICDs. • Support groups are effective tools for parents and other family members and friends who are affected by the patients' disease as well. Examples of support groups: ° The Zapper: http://www.zaplife.org ° The Pacemaker Club: http://www.pacemakerclub.com/public/jpage/1/p/Home/content.do ° Familion: http://www.familion.com/familion/patients/resources/resources.cfm. ° Sudden Arrhythmia Death Syndromes: www.sads.org ° Cardiac Arrhythmias Research and Education Foundation: www.longqt.org ° Ramon Brugada Senior Foundation: www.brugada.org ° The National SIDS/Infant Death Resource Center: www.sidscenter.org ° National Society of Genetic Counselors: www.nsgc.org ° Heart Rhythm Society: www.HRSonline.org ° American Heart Association: www.americanheart.org ° Hypertrophic Cardiomyopathy Association: http://www.4hcm.org/ ° Children's Cardiomyopathy Foundation: www.childrenscardiomyopathy.org ° Hannah Wernke Memorial Foundation: http://www.hannahwernkememorialfoundation.com/

against fatal arrhythmias, many of the devices had never fired. This frustrated many participants, and a similar result was reported in a study by Sherrid and Daubert (2008); discussing, prior to implementation, the possibility that the ICDs would never fire might help ease patients' negative feelings long after undergoing implantation. Much of the literature reports contentment with ICDs regardless of firing; however, Sherrid and Daubert's study, like the present study, examined ICD perceptions in a younger patient population (Kamphuis et al., 2004; Sherrid & Daubert, 2008; Wójcicka et al., 2008). It is possible that patients who are younger and suffering from cardiac channelopathies with minimal symptoms have different outlooks on their health status and the utility of device placement when compared to older patients suffering from congestive heart failure and its associated symptoms. More research is needed in this area to confirm this assertion.

It is important, when providing care to patients with ICDs, to identify those patients who are at increased risk of developing anxiety or depression. Thomas and colleagues identified patients with ICDs and the following characteristics to be at increased risk of developing psychiatric disorders: younger patients, patients who had experienced shocks in the past, and patients who reported current psychological distress or a prior history of psychological distress (Thomas et al., 2006). Since the patient population affected by hereditary cardiac channelopathies is typically younger at age of implantation when compared to the total population of patients with ICDs, this population is inherently at higher risk for developing anxiety, depression, or both. Therefore, screening and treatment for anxiety and depression should be addressed in the care of patients with ICDs.

It is not clear how best to prevent the development of substantial mood disorders in patients and promote positive communication and outlooks. In a randomized clinical trial, patients with ICDs were provided with ICD education and cognitive behavioral therapy for their devices. These patients had reduced physiological levels of cortisol, less psychological distress, and improvements in quality of life (Sears et al., 2000; Sears et al., 2007). This study, like others, identified problem-focused, optimistic coping strategies as the most useful in patients with chronic diseases and patients with ICDs (Flemme, Johansson, & Strömberg, 2012; Hallas, Burke, White, & Connelly, 2010; Kristofferzon, Löfmark, & Carlsson, 2005; Lindqvist, Carlsson, & Sjödén, 2004). In addition, holistic practices may be of use in this patient population for easing stress, as exemplified by the meditation exercise described by one participant in this

study. But although meditation exercises may reduce the anxiety surrounding a patient's diagnosis with a familial channelopathy, this should not be interpreted as a reduction in the severity of the patient's disease or in the risk of developing an arrhythmia, possibly fatal.

Given the small sample size and the subanalysis of a larger study, the results of this study are difficult to generalize. However, the results reflect similar findings in the current literature and are suggestive of issues surrounding ICDs that more patients may experience. It is also possible that participants who offered opinions regarding their ICDs more often had negative experiences regarding their own or a family member's ICD. Only one participant included in this subanalysis of the study was less than 21 years of age, making the generalizability to children of this study's findings difficult; however, given the concerns of the parents in this study and this one child, it is likely that other families experience similar concerns. The small sample size and number of participants from a specific geographical region, as well as the large representation of female participants compared with male participants, limit the generalizability of these findings. Additionally, self-reporting is prone to reporter bias. However, the themes identified in this study likely represent concepts and concerns shared by many other patients with ICDs, and should be useful in aiding healthcare providers in their discussions with patients who have ICDs or are contemplating ICD implantation. We offer a final set of suggestions in an effort to improve patient clarity concerning cardiogenetic disease (Table 6).

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Conflict of Interest Disclosure
The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. No conflicts were noted.

Author Contributions
JL carried out the data analysis/interpretation in this study, drafted the article, and performed a critical revision of the article, including statistical analysis. NH was involved in the concept and design of the article, collected the data, and performed a critical revision of the article. MS was involved in the concept and design of the article, performed data collection, and performed a critical revision of the article. TM was involved in the concept and design of the article, performed a critical revision, and approved the manuscript. RM participated in the concept and design of this article, gave a critical revision, and approved the manuscript. CW contributed to the concept and design of the article and data collection, provided a critical revision, and approved the manuscript. SD was involved in the concept and design of the article, provided a critical revision, and approved the manuscript.

Acknowledgments
This work was supported by award RC1HL100756 from the National Heart, Lung, and Blood Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute or the National Institutes of Health.

Abbreviations
BS = Brugada syndrome; CPVT = catecholaminergic polymorphic ventricular tachycardia; ICD = internal cardioverter-defibrillator; LQTS = long QT syndrome; SCD = sudden cardiac death; SIDS = sudden infant death syndrome; SQTS = short QT syndrome; SUDC = sudden unexplained death in childhood; SUDS = sudden unexplained death syndrome

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Impact of an Intensive Cardiology Orientation Program on Confidence of New Fellows

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Objective: We implemented a four-day intensive clinical orientation program in 2004 for cardiology fellows to compare the change in self-assessed confidence of fellows before versus after the orientation.

Background: The transition from an internal medicine residency to a cardiology fellowship can be challenging. There has been limited research on the use of orientation programs to ease this transition.

Methods: New fellows in 2006 and 2007 (N = 13) were prospectively queried immediately before, immediately after, and six months after orientation about their confidence and their support for the orientation program. We retrospectively queried fellows who began their fellowships in 2004 and 2005 (N = 12) by asking them to complete the same questionnaire based on what they recalled feeling immediately before, immediately after, and six months after orientation. Responses to each question were based on a Likert scale from 1 to 7, and a total confidence score was calculated. Retrospective and prospective data were pooled, and nonparametric paired analyses were performed.

Results: Twenty-five fellows were enrolled. Fellows' confidence scores increased after the orientation from 20 to 36 ($p<0.01$). A significant increase was sustained after six months. In addition, at all time points, the fellows supported the orientation program.

Conclusion: An intensive clinical orientation program improved new cardiology fellows' confidence. Support for this program was high, and the findings support continuation and further development of the program.

INTRODUCTION

The transition from residency to fellowship can be challenging. Fellowship trainees need to embrace new responsibilities, learn new skills, and begin to work in a new environment. Furthermore, when clinical responsibilities begin, it can be difficult for subspecialty trainees to attend introductory lectures, potentially making their transition more difficult and conceivably deleteriously affecting patient care. Thus, condensing these introductory lectures into a focused orientation program seems ideal (Lucarelli, Lucey, & Mastronarde, 2007). Although many training programs have orientations, including 50% (Merenstein & Preisach, 2002) to 90% (Brillman, Sklar, & Viccellio, 1995) of family practice and emergency medicine residencies, their curricula vary widely and their impact is largely unknown (Lucarelli et al., 2007). Several small studies of specific orientation programs have been reported. Nielsen, Holland, and Foglia (2003) evaluated an intensive clinical orientation program on 11 obstetrics and gynecology residents (of whom four were new first-year residents), and reported an increase in all first-year resident test scores immediately after the orientation. Levy and Anwar (1979) evaluated an orientation curriculum for new emergency medicine residents by exposing six new residents from one emergency medicine program to an orientation curriculum and comparing them to nine new residents from a different yet comparable residency program who did not have exposure to the orientation curriculum. The pre-orientation test scores of the two groups were not significantly different, while the post-orientation test scores of the exposure group were significantly higher. However, a test one year after the orientation showed no significant difference between the groups.

The transition from residency to fellowship has been even less well studied than either the transition from medical school to internship or that from internship to residency (Lucarelli et al., 2007). To the best of our knowledge, there have been no other studies on the impact of cardiology fellowship orientation programs. Montefiore Medical Center's Cardiology Fellowship program instituted an intensive four-day orientation program in 2004. We examined both the impact of that program on fellows' self-assessed confidence and their overall support for the program. Our primary outcome was the comparison of fellows' self-assessed confidence before versus immediately after the orientation.

METHODS

Study Population

We anonymously queried 25 cardiology fellows at Montefiore Medical Center, an urban teaching hospital in New York City, from the years 2004 through 2007. We prospectively surveyed all new fellows in 2006 and 2007 (N = 13) with a questionnaire immediately before, immediately after, and six months after the orientation. We retrospectively surveyed 12 of 14 (86%) fellows who began their fellowships in 2004 and 2005 by asking them to answer the

Table 1 | First-Year Fellows' Orientation Session Schedule.

July 1	July 2	July 3	July 5
7:30–8:30 a.m. Study Questionnaire: **Cardiology Fellows** **8:30–9:30 a.m.** Intro and Expectations: **Program Director, Attendings, AECOM Faculty** **9:30–9:40 a.m.** Break **9:40–10:15 a.m.** Informed Consent: **Attending** **10:15–11:00 a.m.** CCU/Consults: **Attending** **11:00–12:00 noon** Tour of Weiler Hospital How to Be on Call @ Weiler Hospital: **Cardiology Fellows** **12:00 noon** Walk to Jacobi Hospital **12:15–1:00 p.m.** Lunch: **Jacobi Faculty** **1:00–4:00 p.m.** Orientation **4:15–5:00 p.m.** Tour of Jacobi How to Be on Call @ Jacobi: **Cardiology Fellows** **5:00 p.m.** Evening "on call." One to two new fellows will shadow the on-call fellow for 3–4 hours at Weiler and Montefiore. Each fellow will shadow once during orientation.	**8:00–8:30 a.m.** Intro and Expectations: **Attendings, MMC Faculty,** CT Surgery Staff Welcome **8:30–9:45 a.m.** **Tour of MMC/NCB** How to Be on Call @ Montefiore & North Central Bronx; Intro to Rotations from a Fellow's Perspective; Computer/Codes: **Cardiology Fellows** **9:45–10:00 a.m.** Break **10:00–11:00 a.m.** Practical Use of the "911" System; Research Studies; **Chief Fellow, Various Attendings** **11:00–11:15 a.m.** Break **11:15–12:00 noon** IABP: **Fellows** **12:00–1:00 p.m.** Lunch/Meet the New Fellows **1:00–2:00 p.m.** Arrhythmias 101: **EP Attending** **2:00–2:15 p.m.** Break **2:15–3:45 p.m.** Should This Patient Go to the Cath Lab? Practical Pre/Post Cath Lab Issues: **Attending, Director of Catheterization Lab** **3:45–5:45 p.m.** Common Consults/Practical Issues: **Cardiology Fellows**	**8:00–9:00 a.m.** Pressure Transducer in CCU, Catheter, Recorder System, Calibration: **Attending** **9:00–10:00 a.m.** Arrhythmias 201: **EP Attending** **10:00–10:15 a.m.** Break **10:15–12:00 noon** Pacemaker 101: **EP Attending** **12:00–1:00 p.m.** Lunch/Meet the New Fellows **1:00–2:00 p.m.** Practical Approach to Echo: **Echo Attending and Staff** **2:00–4:00 p.m.** Hands-on Echo; Teaching Cases: **Echo Attending, Senior Fellow, and Sonographer** **4:00–5:00 p.m.** X-Ray Techniques in CCU and Cath Lab, Practical Points: **Attending, Director of Catheterization Lab** **5:00–5:45 p.m.** Mandatory Written Radiation Exam: **New Fellows**	**8:00–8:45 a.m.** Acute CHF Assessment and Management: **Attending** **8:45–11:00 a.m.** SGC and Fellowship Issues: **Attending** **11:00–12:00 p.m.** Ongoing Clinical Studies Summary: **Faculty** **12:00–1:30 p.m.** New fellows: Please get lunch and return to fellows' office by 12:30 p.m. Physical Exam Review: **Attending** **1:30–2:05 p.m.** EKG–Urgent Issues**:** **Cardiology Fellows** **2:05–2:15 p.m.** Break **2:15–3:30 p.m.** Practical Pacemaker Points and Programming Introduction; Temporary Wires; Common Scenarios: **Cardiology Fellows** **3:30–5:00 p.m.** Wrap-up with Chief Cardiology Fellows; Fellows' Office; Review Key On-call Issues: Back-up, "911," Passwords, Sheaths, etc.… Study Questionnaire

Abbreviations: EP=Electrophysiology, CT=Cardiothoracic, MMC=Montefiore Medical Center, NCB=North Central Bronx, CCU=Coronary Care Unit, IABP=Intra-Aortic Balloon Pump, SGC=Swan Ganz Catheter, CHF=congestive heart failure

same questionnaire recalling what they felt immediately before, immediately after, and six months after orientation. The retrospective group was surveyed on average 10 +/- 6 months after beginning their fellowships. We were unable to reach two of the 14 fellows (14%). This study was approved and exempted by the Montefiore-Einstein Institutional Review Board.

Orientation Sessions

During the orientation program (Table 1), cardiology faculty members gave didactic sessions on core cardiology topics, including arrhythmias, acute congestive heart failure assessment and management, practical cardiac catheterization lab issues, informed consent, X-ray techniques in the coronary care unit and catheterization lab, and pace-

maker and defibrillator basics. Senior cardiology fellows presented didactic sessions on intra-aortic balloon pumps, urgent electrocardiogram issues, common consults, and practical pacemaker programming. There were also hands-on sessions on the use of echocardiography machines and pacemaker and defibrillator interrogation devices.

Study Questionnaire

The study questionnaire (Table 2) was separated into two categories of questions: confidence in medical skills and management of cardiology issues (questions 1–7), and support for the orientation program (questions 8–9). The questionnaire assessed confidence in starting the fellowship, being on call, managing congestive heart failure, interpreting arrhythmias on electrocardiograms, performing trans-thoracic echocardiograms, performing device (pacemaker and defibrillator) interrogations, and approaching ST-elevation myocardial infarction. The questionnaire assessed the fellows' support for the orientation program by asking both whether the orientation would help their fellowship experience and what their overall support for the orientation program was. The responses for each question were graded on a Likert scale of 1 through7, with 1 representing the least agreement with the statement, 4 being neutral, and 7 representing the most agreement. For each subject, at each time point, we created a total score for each of the two categories of questions. Thus, at baseline, for the seven confidence questions, the subject's summed score should range from a low of 7, achieved by reporting a score of 1 for each question, to a high of 49, achieved by reporting a score of 7 for each question. Similarly, for the two support questions, the total score could range from 2 to 14.

Statistical Analysis

Retrospective and prospective data were pooled and analyzed together. Median scores were compared. Nonparametric paired analyses were performed with the Wilcoxon Rank Sum test.

RESULTS AND DISCUSSION

Twenty-five fellows were enrolled over four years. There was a significant increase in the median score for questions assessing confidence from before to immediately after orientation (Table 3, 22 vs. 36, $p<0.01$), and this difference remained significant six months after orientation (Table 4, 22 vs. 38, $p < 0.01$). There was high support, but a non-significant difference in overall support, for the program before, immediately after, and six months after the orientation, with median scores of 13 in each case. When analyzing the retrospective and prospective data separately, the findings for both confidence and support did not significantly differ.

Our findings support that an intensive four-day clinical orientation program increased new cardiology fellows' self-assessed confidence and that this increase persisted six months after the original orientation program. To the best of our knowledge, no such assessment of a cardiology fellowship orientation program had previously been reported. We also found that fellows' support for our intensive orientation program was high immediately before, immediately after, and six months after orientation. This suggests that fellows' support for the program is sustained over time, even after confidence levels have improved.

We believe the high level of support immediately before the program may have been secondary to the new fellows' desire to learn more about both cardiology and the medical system they were joining. We were encouraged that six months after settling into their fellowships, the fellows' support for the orientation program remained high, suggesting that it had utility for them.

Trainee support for an intensive, clinically focused orientation has been documented. At the University of Florida in Gainesville, a trial five-day orientation program for two groups of five first-year obstetric and gynecologic residents reviewed clinical skills and basic procedures. All participating residents strongly recommended that the orientation program be permanently incorporated into the training program (Duff, 1994). In Nielsen et al.'s 2003 study of an intensive orientation program for obstetric and gynecology residents, 64% of the residents rated the program "very helpful" even though seven of the 11 participants were second- and third-year residents. Each resident recommended that the orientation program be offered annually. Furthermore, Lucarelli et al. (2007) reported that an intensive, single-center orientation program in pulmonary and critical care focusing on didactic and procedural skills

Table 2 | Study Questionnaire.

1. I feel confident as I start my cardiology fellowship.
2. I feel confident performing a basic trans-thoracic echocardiogram.
3. I feel confident performing a basic pacemaker interrogation.
4. I feel confident about understanding how to be on call.
5. I feel confident approaching the typical patient with congestive heart failure.
6. I feel confident interpreting arrhythmias on an electrocardiogram.
7. I feel confident about coordinating care for an ST elevation myocardial infarction.
8. The orientation program will help me with my cardiology fellowship.
9. I support having an intensive orientation program.

Table 3 | Pre-orientation versus Immediate Post-orientation Scores.*

	Pre-orientation	Immediate Post-Orientation	P-value
Confidence (Q1–Q7 pooled)	22 (12,28)	36 (31,38)	<0.01
Support for Program (Q8 & 9 pooled)	13 (11,14)	13 (11,14)	NS

*Data reported as median (interquartile range). Q = questions, NS = not significant.

Table 4 | Pre-orientation versus Six-Month Post-orientation scores*

	Pre-orientation	Six months post-orientation	P-value
Confidence (Q1–Q7 pooled)	22 (12,28)	38 (35,40)	<0.01
Support for Program (Q8 & Q9 pooled)	13 (11,14)	13 (10,13)	NS

*Data reported as median (interquartile range). Q = questions, NS = not significant.

improved fellows' self-assessed readiness for clinical and procedural duties. However, the methods and data from that study were not described. Supplementing these data, our results appear to support both that study's findings and the benefits of continuing such intensive clinical orientation programs.

The optimal content of an orientation program for medical trainees, and specifically for a cardiology fellowship program, has yet to be determined. According to Bandaranayake (1985), the curriculum for an orientation program should be designed to address assessed needs and established goals. However, this is often not the case. A survey of 100 family practice residency programs reported that while program directors prioritized social events when organizing orientation programs, new residents highly desired that clinical education be part of the curriculum. Ninety-nine percent of the orientation programs provided a social event with faculty, while only 16% had organized clinical activities with knowledge testing to assess and evaluate the clinical needs of their trainees (Grover & Puczynski, 1999). In order to address the clinical needs of cardiology fellows, our orientation focused on field-specific clinical skills, while also addressing the Accreditation Council for Graduate Medical Education core competencies through both didactic and practical teaching. Although we agree that the social aspects of orientation are important, we subjectively found that there were ample opportunities for fellows and faculty to interact in an informal manner during our program.

The optimal duration of an orientation program is also unclear. Some trainees desire a longer orientation program in fields requiring both clinical and procedural training. In Nielsen et al.'s 2003 study, obstetric and gynecology residents underwent a half-day orientation consisting of multiple didactic and hands-on clinical skills stations. However, the residents did not feel that enough time was allotted for each station and specifically commented on the need for more hands-on time. In the survey by Lucarelli et al. (2007) of 87 fellowship programs in pulmonary and critical care, 86% had formal orientation programs. These programs consisted, on average, of five to 10 hours of didactics and up to five hours of wet-lab training. In contrast, our curriculum devoted more hours to both didactics and hands-on sessions. Further study is required to optimize the duration and the content of such programs.

Studies in surgical residency programs (Pandya, Bhagwat, & Kini, 2010; Pandya, Bhagwat, & Kini, 2012; Fernandez et al., 2012) found that intensive orientation programs yielded improvement in clinical skills. Although our findings were limited to self-assessed confidence and to support for the orientation program, the studies by Pandya et al. (2010, 2012) and Fernandez et al. (2012) suggest that focused orientation programs may yield clinical benefit. Further study in a wider range of medical fields is warranted.

Strengths of our study include its relatively larger sample size as compared to previously reported studies of medical residency or fellowship orientation programs, its assessment of multiple fellowship classes, and its six-month follow-up. There are several limitations. Our measure of confidence was subjective and not previously studied, and we did not have a control group. Data from 12 subjects were collected retrospectively, which may have led to influence by recall bias. However, the subjects were instructed to answer the questions as if they were new fellows. Also, when the retrospective and prospective data were analyzed separately, the findings did not significantly differ.

CONCLUSION

In an area lacking published data, we found that an intensive orientation program for new cardiology fellows improved

self-assessed confidence in field-specific clinical skills both immediately and six months after orientation. Our findings support the continuation of such programs, the need for further study of their optimization, and further evaluation of whether they may yield patient-care benefits.

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Conflict of Interest Disclosure
The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. No conflicts were noted.

Author Contributions
All authors had an equal role in the writing of the article.

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Commensal Microbiota: Powerful Immunological Tools for Gut Homeostasis

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In recent years, several important findings in the fields of gut microbiology and immunology have emerged. An increasing number of studies have investigated the characteristics of commensal microbiota and how their symbiotic relationship with the host can be beneficial for gut health. It is becoming evident that gut microbiota and the intestinal immune system must achieve a complex and delicate balance in order to fight pathogenic bacteria and to protect those that contribute to intestinal homeostasis and functions. Although microbiota diversity is not fully understood, new evidence suggests that commensal colonization is dependent on dietary, environmental, host genetic and immunological factors. In addition, the recent characterization of the structure, function, and diversity of the healthy human microbiome will be extremely useful for further studies focused on clarifying the immunological and physiological roles of commensal microbiota.

INTRODUCTION

Intestinal homeostasis is mediated by cross-talk among intestinal resident cells, commensal microbiota, local immune cells, and metabolites. Unfavorable alterations to these interactions are thought to be responsible for the development of inflammatory bowel disease (IBD). IBD includes two major disorders: Crohn's disease (CD) and ulcerative colitis (UC). While CD can affect the entire gastrointestinal tract, especially the ileum, UC results in an inflammation of only the large intestine or colon. Although it is not easy to define the exact etiology of IBD, at least three different causes have been considered to play a major role: genetic predisposition, environmental factors (including the commensal microbiota and diet), and the immune system.

Recent genetic studies on IBD patients have shown around 100 different loci that could participate in the development of IBD. Polymorphisms of genes encoding for IL-23R, NOD2, beta defensin-2, and IRGM are considered to be most commonly associated with the development of inflammatory bowel disorders (Fellermann et al., 2006). Although mutations in these genes, which regulate primarily intestinal barrier functions and mucosal immune responses, have been found to modulate IBD susceptibility, they cannot be employed as predictors of disease.

Increasingly, findings underline the essential role of commensal microbiota in the maintenance of gut homeostasis for at least three major reasons. First, all microbiota deliver trophic and mechanical signals for conducting essential metabolic processes, including bond breaking, nutrient release, and vitamin production, and for enhancing barrier epithelial functions (Sansonetti & Medzhitov, 2009). Second, they prevent colonization of pathogenic opportunistic microorganisms. Third, they actively stimulate the immune system by enhancing the body's defense against pathogens and by maintaining peripheral immune tolerance against all the potential antigens present on the lumen (Mazmanian, Round, & Kasper, 2008). All these microbiota functions occur only through constant mutualism with the intestinal immune and nonimmune cells.

This review aims to discuss and summarize some of the characteristics and functions of the living organisms that reside in the gut in order to underscore their important roles not only in microbiology and nutrition but also in immunology.

THE COMMENSAL MICROBIOTA

The gut is an organ populated by a complex variety of bacterial communities whose composition determines the activation of both innate and adaptive immune systems (Figure 1). The mammalian gut is the largest surface of our bodies in contact with a bacterial environment. The amount of resident microbiota increases from jejunum through each subsequent part of the gut, reaching up to 10^{12} per gram in the feces. This bacterial community includes more than 1,000 species, and the majority of them are obligate anaerobic organisms (Floch, 2011). Presently, compared to the traditional culture-dependent techniques, new methods, such as genetic screening of 16S rRNA gene and analysis of T cell receptors (Lathrop et al., 2011), have been shown to be more efficient in detecting gut microbiota.

In an adult, most of the gut microbiota belong to two phyla: Firmicutes (Gram-positive anaerobes) and Bacteroidetes (Gram-negative anaerobes), and, to a lesser extent, to the smaller groups of Proteobacteria and Actinobacteria. Indeed, a recent study (Floch, 2011), performed by the National Institutes of Health (NIH) Human Microbiome Project along with the European MetaHIT consortium, demonstrated that, despite the highly complex composition of the commensal microbiota, the gut microbiome is composed of only three major enterotypes irrespective of host age, gender, and body mass index (Arumugam et al., 2011). Therefore, these data suggest that in our guts there is a "limited number of well-balanced host-microbial symbiotic states" (Arumugam et al., 2011). The authors observed that microbiota composition can significantly change in individuals who are developing disorders such as IBD and

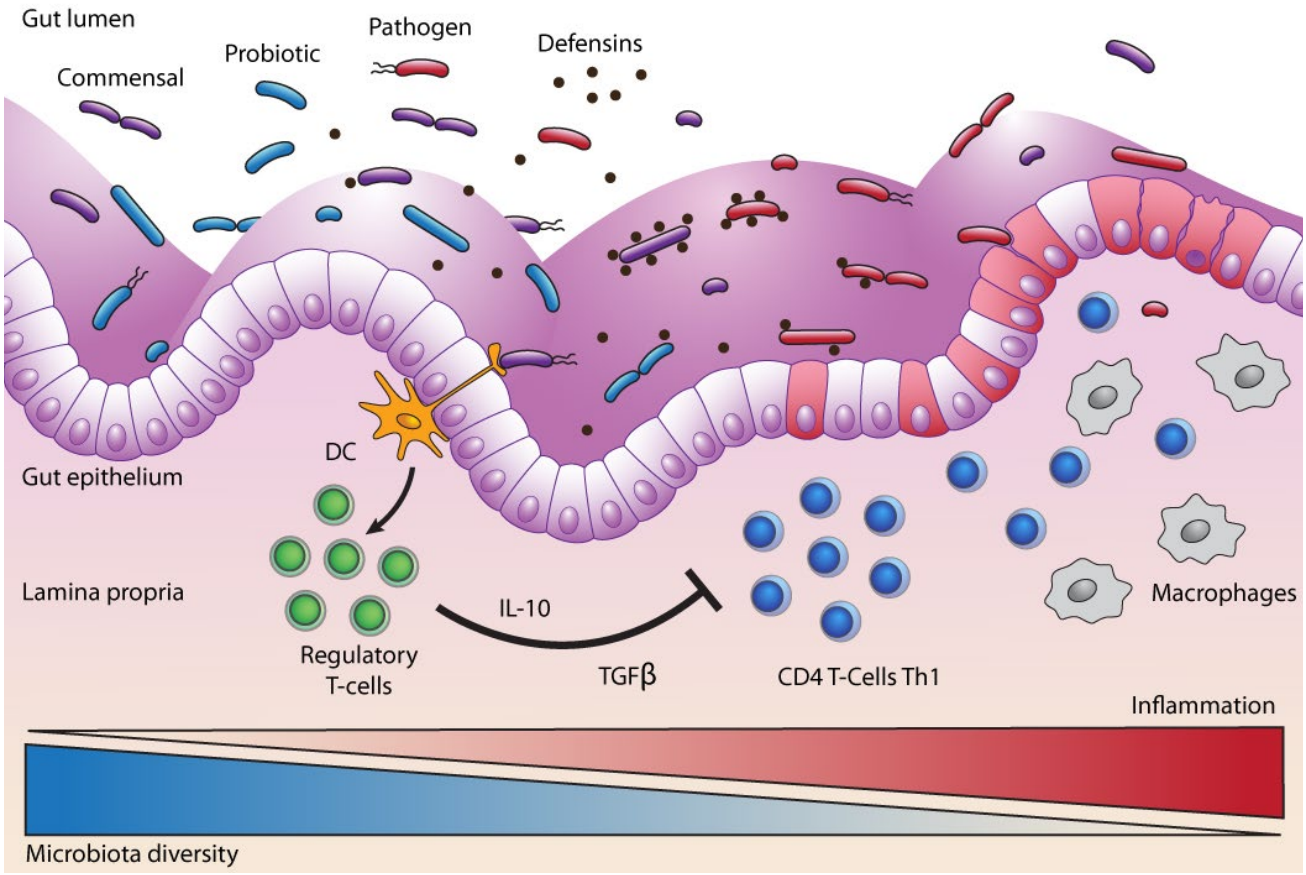

Figure 1 | A wide diversity in intestinal commensal bacteria promotes intestinal health. The gut is populated by a large community of microorganisms, called "commensal bacteria" or "intestinal microbiota," that maintain gut health by increasing digestive efficiency, preventing inflammatory processes, modulating immune response, and precluding the entry of pathogens into the lamina propria. This community is numerous, reaching up to 10^{12} bacteria in the colon, and extremely heterogeneous, containing more than 1,000 different species. In a healthy intestine (left half of the figure) the level of inflammation is very low. Commensal bacteria can be sensed by dendritic cells or epithelial receptors. This generates an expansion and activation of regulatory T cells that produce anti-inflammatory cytokines such as IL-10 and TGF-b. Those cytokines inhibit the activity of pathogenic CD4T-Cells Th1 and macrophages and promote the release, into the lumen, of anti-inflammatory products such as defensins or IgA, which prevent pathogen bacteria entry. Additional help for the maintenance of the gut's immune balance can be obtained through the introduction of probiotics. Probiotics are known to mimic commensal bacterial and to stimulate the gut's immune system, although their exact role is still under investigation. By contrast, a diet rich in fats and sugars, antibiotic treatments, or other environmental factors can strongly reduce microbiota diversity and therefore compromise gut health and encourage inflammation (right half of the figure).

obesity (Arumugam et al., 2011).

Colonization of the intestine begins at birth, either from the immediate exposure to the mother's vaginal microrganisms or later from feeding. *Bifidobacteria*, belonging to the Actinobacteria phylum, and *Lactobacillus,* a component of the Firmicutes phylum, are established early after natural delivery; however, these species are often late arrivals in the case of Caesarian delivery (Floch, 2011). It has been reported that in breast-fed infants, *Bifidobacteria* are the predominant species; conversely, in formula-fed infants, *Bacteroides*, belonging to the Bacteroidetes phylum, have been found to predominate. As soon as children switch to regular food, the flora assumes the composition and complexity of that of an adult (Floch, 2011).

DIETARTY IMPACT ON GUT MICROBIOTA

Many studies have clearly demonstrated that dietary habits are one of the major factors that modulate the gut microbiota (Turnbaugh et al., 2009; De Filippo et al., 2010). In particular, a recent study comparing the gut microbiota composition of children living in a rural African village to that of those living in an industrialized area in Italy demonstrated a remarkable connection between bacterial composition and diet (De Filippo et al., 2010). In the studies described in this elegant paper, the authors found that children fed with a traditional rural African diet, which is low in fat and animal proteins but rich in starch, fibers, and plant polysaccharides, had higher concentrations of Actinobacteria and Bacteroidetes, whereas children fed with a diet richer in sugar, animal fat, and calories (a diet typical of industrialized countries) have a predominance of Firmicutes and Proteobacteria (De Filippo et al., 2010). Another study reports that the ratio of Firmicutes to Bacteroidetes (F/B) increases in obese humans (Ley,

Turnbaugh, Klein, & Gordon, 2006). However, it is still controversial whether there is a correlation between F/B ratio and obesity (Ley et al., 2006; Arumugam et al., 2011) and whether this ratio can be interpreted as a potential obesity predisposition factor.

Dietary fibers contain xylan, cellulose, xylose, and carboxymethylcellulose, which can be converted into short-chain fatty acids (SCFAs) (Flint, Bayer, Rincon, Lamed, & White, 2008) and have been proven to have a protective role against gut inflammation (Scheppach & Weiler, 2004). De Filippo et al. (2010) found that children from rural Africa with diets rich in plant polysaccarides and low in sugar have abundant SCFA in their feces. This indicates that those dietary conditions could specifically select SCFA-producing bacteria (De Filippo et al., 2010; Maslowski & Mackay, 2011), which might prevent the establishment of potentially pathogenic intestinal microorganims (Hermes et al., 2009). Ultimately, mice that are raised in the absence of microbiota (under germ-free conditions) have an impaired concentration of SCFA (Høverstad & Midtvedt, 1986), and succumb to inflammatory immune disorders (Maslowski et al., 2009; Chervonsky, 2010). These data suggest that diet not only can contribute to the maintenance of a healthier microbial composition, but also can modulate inflammatory responses.

THE "HYGIENE HYPOTHESIS"

Commensal biodiversity in the gut can be considered an essential marker for healthy individuals. This microbiota biodiversity can be strongly altered and damaged through ingestion of drugs (e.g., antibiotics, vaccines), during clinical treatments, by improving sanitation, by food composition, and by other environmental factors. Limited contact with microorganisms from the external environment defines what has been called the "hygiene hypothesis" (Strachan, 2000). This term refers to the increasingly common phenomenon, occurring especially in Western countries, of the use of extreme cleaning methods, including excessive hand- or food-washing and intensive sterilization techniques, that drastically reduce the chance for our bodies to encounter microorganisms. While treatments are considered effective for preventing contact with pathogens and toxins, from another perspective they limit contact with microorganisms that could beneficially stimulate components of the innate and adaptive immune systems.

The innate immune system represents the first line of defense for our bodies, especially against infections, but it does not provide a specific or long-lasting immune reaction. Therefore, a second type of defense system, called an "adaptive immune system," is needed to recognize specific antigens and to stimulate more-robust and long-lasting immune processes that can also be remembered throughout life. One of the most important cell types of the adaptive immune system is T cells. On their surfaces, T cells express receptors ("T cell receptors," or TCRs) that bind to specific antigens presented by a group of molecules called a "major histocompatibility complex" expressed on antigen-presenting cells. Classically, an individual's TCR specificities are defined through the self/nonself discrimination processes during thymus development. Inadequate microbial stimulation, especially during childhood, is believed to impair inflammatory T helper 1 (Th1) responses, with a resulting predominance of T helper 2 (Th2)-mediated cytokines such as IL-4, IL-5, and IL-13, which are known to be implicated in the development of allergies (Strachan, 1989; Maslowski & Mackay, 2011). Diseases such as asthma and allergies are extremely rare in several rural African areas (Maslowski & Mackay, 2011). Further, genetic screening of the commensal microbiota has demonstrated that the reduction of biodiversity is also associated with inflammatory conditions such as diabetes and obesity (Arumugam et al., 2011), and with an increased risk for food allergies (Peterson, Frank, Pace, & Gordon, 2008; Sokol et al., 2008).

COMMENSAL BACTERIA ARE ACTIVE ENHANCERS OF GUT IMMUNE TOLERANCE

Food is a complex mix of many potential antigens; however, only a minimal amount (1% to 2%) is adsorbed through the mucosa in the antigens' intact immunogenic form. Therefore, maintaining tolerance against those potential antigens is one of the major defense mechanisms for the prevention of inflammatory bowel diseases. There are at least three different ways to maintain tolerance in the gut: first, by active immune suppression of immune responses through regulatory T cells (Tregs); second, by evasion of immune recognition operated by microbiota; and finally, by production of soluble factors (anti-inflammatory cytokines, IgA, and antimicrobial peptides [AMP] such as defensins). Recent studies have demonstrated that commensal bacteria participate in all of these defense mechanisms (Sansonetti & Medzhitov, 2009).

Active suppression can be mediated by bacteria through stimulation of Tregs, which are the most important immune T cells aimed at suppressing immune responses to microbe-triggered intestinal inflammation. For instance, it has been reported that several species of bacteria such as *altered Schaedler flora* resulted in a de novo expansion of mucosal Tregs in the colon lamina propria (Geuking et al., 2011). It seems that the encounter with commensal microbiota results in an increased generation of Tregs in the intestine rather than an induction of proliferation of pathogenic effector T cells (such as Th1 cells) that could deliver inflammatory signals. Thus, these data suggest that microbiota colonization–induced Treg cell responses are an essential intrinsic mechanism to promote and maintain host-intestinal microbial T cell interactions (Geuking et al., 2011). In addition, Lathrop and colleagues were able to demonstrate that those colonic Tregs express T-cell receptors different from those employed by Tregs in other body sites, suggesting a post-thymic education of immune cells in the periphery driven by commensal microbiota (Lathrop et al., 2011).

The escape from immune recognition can occur through a failure in the expression of virulence factors such as pathogen-associated molecular pattern receptors (PAMPs), includ-

ing lipopolysaccharide and peptidoglycan. It is still not clear if the diversity on the expression level of PAMPs between commensal and pathogenic bacteria can be considered a crucial mechanism that the immune system uses to distinguish between the two bacterial categories. PAMPs trigger a wide variety of pathogen-recognition receptors (PRRs), either extracellular, such as Toll-like receptors (TLRs), or intracellular, such as nucleotide-binding oligomerization domain receptors (NODs), both expressed on intestinal epithelial and immune cells (Maloy & Powrie, 2011). Basal activation of PRRs that leads to stimulation of intracellular pathways is essential to preserve intestinal cell homeostatic processes. These stimulated responses can include, for example, intestinal epithelial cell proliferation caused by the increase of anti-apoptotic factors, induction of tissue repair mechanisms, and production of protective factors such as AMPs—defensins and RegIIIγ, for example (Vaishnava, Behrendt, Ismail, Eckmann, & Hooper, 2008; Asquith, Boulard, Powrie, & Maloy, 2010; Maloy & Powrie, 2011).

Bacteria sensing is thought to induce a constant and necessary minimal level of "physiological inflammation" to ensure the health of our intestines throughout our lives. Any defects in bacterial sensing can lead to bacteria penetrating into the lamina propria, triggering substantially larger inflammatory immune responses. This hypothesis was widely demonstrated by different studies that used mice deficient in some TLRs, such as TLR4-/- mice (Rakoff-Nahoum, Paglino, Eslami-Varzaneh, Edberg, & Medzhitov, 2004) and TLR-5-/- mice (Vijay-Kumar et al., 2007), or mice that do not express protein involved in their downstream activation pathways, such as Myd88-/- mice (Rakoff-Nahoum et al., 2004). All these groups of mice have been reported to be highly sensitive to dextran sodium sulphate–mediated colitis (Rakoff-Nahoum et al., 2004), and about 30% of TLR-5-/- mice spontaneously develop severe gut inflammation with prolapse development (Vijay-Kumar et al., 2007). In the same way, activation of NOD receptors leads to the activation of transcription factor NF-kB and mitogen-activated protein kinase (MAPK)-pathways. Those pathways are highly modulated during different immune responses, including oxidative stress, inflammation, and bacterial or viral infections (Sansonetti & Medzhitov, 2009). The importance of these activation signallings in the protection against intestinal inflammation has been demonstrated in Crohn's disease patients with mutations in the *NOD2* gene that result in an impaired activation of NF-kB (Strober, Murray, Kitane, & Watanabe, 2006). Moreover, mice that do not express NLPL13, a protein belonging to the NOD family of receptors, also succumb to acute models of colitis (Zaki et al., 2010). All these findings indicate that the activation of PRRs by commensal bacteria is a necessary signal to coordinate intestinal immune responses. However, it is unknown how PPRs are able to differentiate between commensal and pathogenic bacteria and deliver different signals to the gut immune cells.

Finally, production of soluble factors, including anti-inflammatory cytokines such as IL-10 and TGF-b and AMP molecules such as defensins, as potent tolerance inducers in the gut has been evaluated (Sansonetti & Medzhitov, 2009; Maloy & Powrie, 2011). Defects in the production of antimicrobial peptides increase the bacterial invasion, leading to subsequent inflammation. In addition, a specific subset of dendritic cells that express CD103 can stimulate Tregs to produce anti-inflammatory factors such as TGF-b or retinoic-acid (Coombes & Powrie, 2008). While in mice, IL-10 deficiency results in a spontaneous development of colitis (Berg et al., 1996), in human beings, mutations in IL-10 receptor genes *IL10RA* and *IL10RB* have been recently found to aggravate IBD (Glocker et al., 2009). Likewise, exposition of *Bacteroides fragilis* protects us against the colitis induced by *Helicobacter hepaticus* through the stimulation of the anti-inflammatory cytokine IL-10 by intestinal immune cells (Mazmanian et al., 2008). *Clostridium* species also have been shown to actively promote IL-10 production (Atarashi et al., 2011).

Taken together, these findings indicate that gut homeostasis depends on maintaining the balance among all three major defense mechanisms that the gut uses: active immune suppression of immune responses by Tregs, microbiota immune recognition-evasion, and the production of soluble factors. Commensal bacteria are shown to be an essential component for gut health through all these mechanisms.

THERAPEUTIC EXPLOITATION OF COMMENSAL MICROBIOTA

If commensal bacteria are indeed important for the regulation of immune responses, they represent a novel area for therapeutic intervention in microbial imbalance (dysbiosis) conditions. Probiotics are "living microorganisms that, upon ingestion in sufficient numbers, exert health benefits" (Schrezenmeir & de Vrese, 2001). They can be included in dietary products such as yogurt. After oral administration, they are expected to survive the low pH in the stomach and to colonize the mucosal surfaces of the colon, albeit for a short period.

The most-common probiotic bacteria belong to the *Lactobacillus* and *Bifidobacterium* species, and they have been shown not only to improve and regulate immune-system responses but also to have a positive influence on the preexisting microflora stability, to inhibit pathogen colonization, and to enhance mucosal trophic mechanisms by stimulating intestinal epithelial cell barrier responses. As probiotics express PAMPs, they are thought to mimic the function of commensal bacteria by engaging and activating the PRRs on the epithelial mucosal surfaces. Confirmations of immunological probiotic functions were demonstrated by *Lactobacillus rhamnosus* and *Bifidobacterium lactis* having increased epithelial resistance, enhancing the phosphorylation of epithelial proteins such as occludin and ZO-1 (Mathias et al., 2010). Heat-shock proteins are constitutively expressed on epithelial cells and, under stress conditions, regulate the epithelial homeostasis (Petrof et al., 2004). It has been shown that the probiotic *Lactobacillus GG*

releases soluble factors that have a cytoprotective effect by stimulating synthesis of heat-shock proteins in intestinal epithelial cells through p38 and MAPK pathways (Tao et al., 2006). Many other natural anti-inflammatory properties have been described for probiotics, ranging from the capacity to increase lymphocyte proliferation to the stimulation of innate and adaptive immune responses, including IL-10 production. While some *Lactobacilli* strains are able to increase phagocytotic processes in macrophages (Maassen, 1999) and to stimulate the secretion of lysosomal enzymes (Perdigon, de Macias, Alvarez, Oliver, & de Ruiz Holgado, 1986), other strains have been found to regulate the production of pro-inflammatory cytokines, including IL-4 and IL-12 (Sütas, Hurme, & Isolauri, 1996). All these findings suggest that probiotics can stimulate both adaptive and innate immune responses. Ultimately, probiotics can be used not only to reinforce the natural mucosal barrier defenses but also to prevent an imbalance between pro-inflammatory and anti-inflammatory cytokines. Although the efficacy of probiotics in clinical trials for ulcerative colitis patients is promising, clinical trials in Crohn's disease patients have not inspired much enthusiasm (Shanahan, 2010).

In the last decade, an unconventional therapeutic approach has been used to treat a severe case of intestinal dysbiosis. This technique, called "fecal transplantation," aims to introduce microbes isolated from a donor gastrointestinal tract to the dysbiotic patient in order to establish more "normal" commensal flora. The pioneer of fecal transplantation is Dr. Lawrence Brandt (chief emeritus of gastroenterology at Albert Einstein College of Medicine), and so far his results have been quite encouraging (Palmer, 2011). Nevertheless, more studies need to be completed before we can fully understand the exact mechanisms that underlie the beneficial host-microbe interactions that seem to be established in those therapeutic approaches.

CONCLUSION

Current studies regarding the interaction between commensal bacteria and gut immune and nonimmune cells suggest that gut microbiota are not ignorant bystanders in our intestines; they are one of the major contributors to the maintenance of intestinal homeostasis. Through these essential and constant host-microbial interactions, the overall digestive functions are maintained. Microbiota protect against infection because they can compete with opportunistic and pathogenic bacteria, but they also break down and digest food and stimulate cell-defense mechanisms. It is extremely important to maintain the balance among bacterial species. This bacterial biodiversity depends on the characteristics of the bacteria themselves and on the environment, including nutrition, tissue repair, and physiological processes. While low commensal bacteria biodiversity facilitates the entrance of pathogens, high microbiota diversity provides optimal conditions for a healthy digestive system.

There is still much to learn about how commensal bacteria regulate intestinal homeostasis. Understanding the regulation of mucosal immune responses to gut microbiota may be the key to targeted manipulation of immune cell–mediated responses, of nonimmune cell–mediated processes, and of microflora composition. Genetic approaches that could modify bacterial flora to selectively enhance the production of anti-inflammatory cytokines (e.g., IL-10) or antimicrobial peptides (e.g., defensins, RegIIIg) have already been considered as therapy for IBD patients (Steidler et al., 2003). However, improvements and combined studies on all the components of the digestive system, on their distinct functions, and on their cross-talks could create a successful strategy to treat intestinal inflammatory diseases.

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Conflict of Interest Disclosure

The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. No conflicts were noted.

Acknowledgments

The author thanks the anonymous reviewers of the manuscript of this article for their thoughtful comments and revisions. The author would also like to thank Lorenzo Agoni, MD, PhD for designing the manuscript's figure.

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What Have We Learned About Learning? Reflections from Developmental Psychology and Cognitive Neuroscience

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Learning is thought to be something at which human beings excel. They learn many things over the course of time from infancy to adulthood, such as how to communicate with others using language, how to manipulate objects, and how to solve problems effectively. But what is the science behind learning? How do people's brains change as they learn, and does this have anything to do with the strategies they use to learn? In this essay, we briefly outline the changes in how researchers approach the issue of learning across development, with a focus on language learning, and discuss how current neuroscientific research complements what is known behaviorally about learning. We illustrate how various developmental and neural processing inputs interact with prior experience to facilitate learning. Further, the contributions of active learning over the lifespan, and the roles of novelty and motivation in enhancing learning, are considered. Approaching learning as a complex, multifaceted process will help researchers move toward more-integrated behavioral and neurobiological models of learning.

INTRODUCTION

Human knowledge ranges from the marvelous to the mundane; a mind that can unravel the mysteries of particle physics can also understand how to make a cup of tea. And yet we are born without knowing how to do either of these; we learn such knowledge and skills through our experience with the world. Throughout childhood we encounter and acquire language, learn how to manipulate objects, and represent complex events from our environment. These are far from simple tasks. Yet infants achieve this kind of learning with relative ease. Societal interest in enhancing early learning has increased considerably in recent years, as evidenced by the remarkable popularity of infant learning products such as "Baby Einstein" and "Baby Bright." Alison Gopnik, a professor of psychology at Berkeley, suggests that this early capacity for learning may be what has provided human beings with an evolutionary advantage over other species (Gopnik, 2010). Here, we consider how learning may progress across the lifespan, extending from infancy and childhood into the adult years. We explore differences in accounts of learning across development while also highlighting similarities, such as the need for active engagement during learning. Accounts of the neural underpinnings of learning, through plasticity and dopaminergic learning models, are outlined briefly. These findings point toward the complexity of human learning as a multifaceted phenomenon extending across the lifespan.

DIFFERENCES IN LEARNING AND NEURAL PROCESSING ACROSS DEVELOPMENT

In the scientific world, neurological evidence is thought to exist for differences in learning between children and adults. Damage to the brain in adulthood, affecting the language networks, typically results in aphasia—an impairment of the ability to use language. However, the severity is markedly less if the injury occurs before or immediately after birth (Lennenberg, 1967; Bates, 1999). The outcomes of left-hemisphere injury are less debilitating in children with perinatal focal lesions than when such injuries occur in adults, suggesting that at some point between birth and adulthood the way we learn language changes. Converging evidence suggesting a difference between adult and child language-learners is derived from behavioral studies. These suggest that it becomes harder over time to learn a foreign language (Johnson & Newport, 1989). However, there is considerable debate about how long this time frame is (Flege, Munro, & MacKay, 1995; Flege, Yeni-Komshian, & Liu, 1999; Zevin, 2012), and how individual differences may contribute to this difficulty. In addition, there are disputes about what aspects of language (syntax, pronunciation, vocabulary), are harder to learn after this time frame. For instance, categorizing speech sounds in a second language is more difficult in adulthood than it is earlier in development (Kuhl, 2004; Werker & Tees, 2005; Zevin, 2012). Little is known about where the boundaries of a "sensitive period" for learning language lie and how this period might relate to neural changes over development.

Can a consideration of these neural changes over development then serve to explain changes in learning, and perhaps this sensitive period? Many studies have shown that there are structural and functional neural changes over childhood and adolescence (Giedd et al., 1999; Lu et al., 2007; Sowell et al., 2004; Shaw et al., 2008), including changes in cortical thickness and white-matter volume, as well as structural and functional connectivity. These changes can be a result of age; for instance, cortical thickness changes as a result of age (Shaw et al., 2008), but can also relate to expertise and learning. Cortical thickness in the inferior frontal gyrus is related to grammatical proficiency (Nuñez et al., 2011) and phonological proficiency (Lu et al., 2007). Experience with a second language, as indexed by age of acquisition, can modulate the degree of structural neural reorganization. The earlier a second language is learned, the higher is the gray-matter density (i.e., the relative concentration of cell bodies, dendrites, axons, and glia in cortical volumes)

in the left inferior parietal region (Mechelli et al., 2004). But even in monolinguals, proportional changes in the gray-matter density in the posterior supramarginal gyri bilaterally can be correlated with number of words learned (Lee et al., 2007). These findings demonstrate how neural changes can be bidirectional, with changes occurring in neural structure via learning and not simply as a result of maturational processes.

Neurobiologists today accept the idea of pluripotentiality—the capability of the cortex to take on a wide array of representations. In childhood, there may be early competition among neural areas for control over various behavioral tasks; regions that process tasks efficiently will win (Elman et al., 1996; Siegel, Donner, & Engel, 2012). Systematic functional neural changes might occur with expertise relating to a skill or an over-rehearsed task, resulting in either an increase or a decrease of neural activity within regions or changes in the network of regions involved in a task. Brown and collaborators (2005) demonstrate developmental changes in cerebral functional organization, from the ages of 7 to 32, for the relatively simple task of word generation. For this task, more cortical areas were recruited at younger ages, with greater involvement of prefrontal regions earlier in life. The process may thus be one of interactive specialization: neural processing in childhood may be diffuse in several regions across both hemispheres, and may become increasingly task-specialized and restricted to more-specific networks as expertise builds (Durston et al., 2006; Karmiloff-Smith, 2010). There is also event-related potential evidence supporting this theory: comprehension of single words in infancy (13–17 months) is processed in a more distributed, bilateral manner (Mills, Coffy-Corina, & Neville, 1997), becoming increasingly left-lateralized at 20 months of age. This may serve to explain the difference in the severity of language impairment mentioned earlier, as networks become more focal and specialized in adulthood. In old age, some evidence points to a converse reorganization of language processing (Federmeier, Kutas, & Schul, 2010), perhaps due to cortical atrophy (Tyler et al., 2010).

Further results from the Brown et al. (2005) study also indicate regions where children showed less activation than adults did, such as the lateral and medial frontal cortex and the left parietal cortex, suggesting that these regions were integrated into task-related networks over childhood. This suggests the importance of understanding neural changes, as these are regions typically associated with prolonged developmental courses, coming "online" during adolescence. The role and function of these regions are being explored, and they seem to relate to executive functioning, notably inhibition, attention, and self-knowledge. These neural differences were all observed for the same simple task, even when controlling for performance differences on the task. It therefore seems likely that young children use different neural resources than young adults do while performing the same task, even when their overt behavioral performance is identical. Thus, the neurological picture appears much more complex than that suggested by a "sensitive period," and it seems evident that understanding changes in neural activation will play a large role in illustrating the complex interplay between brain and behavior.

ACTIVE LEARNING STRATEGIES—FROM INFANCY TO ADULTHOOD

Characterizing the behavioral side of the learning process, developmental psychologists have conducted research revealing that babies are sophisticated learners and demonstrating their active role in the learning process. A simple example is the case of producing words; learning label-to-object mappings amid baby paraphernalia and a large number of toys is a challenge. Words are typically produced by many people whose voices vary considerably, and not always in isolation. As an example of the complexity this label-to-object mapping entails, the word "dog" can occur in multiple contexts: when looking at a pet, at a picture book, or in an animated cartoon, and also in reference to many breeds of dogs. It can also occur within nonliteral phrases such as "it's a dog-eat-dog world." To explain how children may learn words and grammar in this "busy world," many developmental psychologists have favored the idea of innate specification of function, perhaps shaped by evolution (Spelke & Kinzler, 2007). This includes the notion that we have special, inbuilt modules and neural mechanisms to help us parse language. The opposite notion is that of a tabula rasa, or blank slate, where the child is taught only through interaction with the environment. As we know from the neurological studies presented above, neither of these explanations is completely correct. However, most current approaches to understanding learning incorporate elements of both these approaches, and the argument may really lie in the relative role the environment plays. One such approach suggests that learning, whether in the visual, perceptual, motor, or language domain, can arise from identifying regularities in the environment around us, without any explicit instruction or even intention to learn (Perruchet & Pacton, 2006). For example, in English, within the phrase "sit down," the combination of the sounds within "sit" or within "down" is more frequent and acceptable than the combination of sounds between the two words—in this case, "tdo." Understanding how likely it is for sounds to be put together within a language may help us learn where word boundaries lie. As the reader may have realized when listening to a foreign language, these are quite difficult to parse in continuous speech. However, we know that adults are able to learn this kind of information within an hour of listening to a new language (Saffran, Aslin, & Newport, 1996), even if the language is stripped of all other cues such as intonation and meaning.

In the past few decades, researchers have made progress by leaps and bounds in our knowledge about what infants can comprehend. Primary evidence has come from studies that work on the principle of novelty-preference: infants look longer at occurrences that are novel. So if they have learned about an occurrence, they should look less at that occurrence, and more at an interesting novel phenomenon. (For a full review of this methodology, and some new

directions, see Aslin, 2007.) Many such studies have shown that even 8-month-olds are able to segment continuous speech—to learn word boundaries, based on the statistical information within the speech stream—with less than two minutes of exposure and no explicit training (Saffran et al., 1996). There is evidence to suggest that infants as young as 2 months can learn regularities over complex visual patterns (Kirkham, Slemmer, & Johnson, 2002). This serves to illustrate that learning mechanisms can be powerful, implicit, and used to understand the world around us from a very young age. Extending the role of these learning mechanisms further, sound sequences that are highly probable within a language are more likely to be accepted as labels for words (Graf-Estes, Evans, Alibali, & Saffran, 2007). This strain of research demonstrates that babies are likely not passive listeners who simply learn the words parents teach them, but that they actively track the information available to them, and can use and generalize this information in other contexts.

Experience differs across children, so they may have different ways of learning the same information. For instance, early in development, monolingual children use a word-learning constraint, the mutual exclusivity constraint (Markman & Wachtel, 1988). This constraint stipulates that an object cannot have more than one name; hence if the child already knows the word "car," he or she will not think that a new word refers to cars. At an early stage of word learning, before children start to learn synonyms, this is likely to be an effective strategy to learn label-to-object mapping. However, recent research (Houston-Price, Caloghiris, & Raviglione, 2010) suggests that bilingual children do not exhibit this phenomenon, as even early on, their experience tells them that two different labels can be used for a single object.

Infants also learn a lot about their environment by their interaction with it, and certain environmental experiences may change the learning of other related skills. This is not a consequence of simple growth, or maturation. The environmental demands infants are exposed to allow them to use the set of cognitive capacities they possess to change their cognitive ability, sometimes even across different cognitive domains. For instance, infants who were unable to grasp objects were given experience with Velcro sticky mittens. This enabled them prematurely to grab objects by simply swiping at them. When tested later, they showed increased visuo-motor coordination, and more mature grasping, than infants who were not given this unusual early Velcro experience (Needham, Barrett, & Peterman, 2002; Barrett & Needham, 2008). This suggests that even very young children use their prior sensory and motor experiences and expectations, when engaging with their environment, to a greater extent than previously believed, and that early experiences may have cascading consequences through development.

This kind of active experience may even be *crucial* for learning in childhood. For example, when children learn from traditional interpersonal interaction with caregivers (as opposed to learning from television programs and educational videos), they are able to learn more (Kuhl, Tsao, & Liu, 2003). Further, they fail to generalize learning from one situation to the next when learning from recorded materials (Christakis et al., 2009). Successful screen learning may require a more dynamic interaction of the infant with the task at hand—for instance, new gaze-contingent training paradigms, which involve the stimulus changing based on where and how long an infant looks, do demonstrate improvements in cognitive control and sustained attention (Dekker, Smith, Mital, & Karmiloff-Smith, in preparation; Wass, Porayska-Pomsta, & Johnson, 2011).

Active engagement with the environment is equally important for adults in facilitating learning. The role of learning within adulthood has emerged as a growing area of enquiry, with particular emphasis on active engagement as a critical learning mechanism. James and collaborators (2002) examined visual learning in adults using a 3D object-rotation paradigm presented within a virtual reality environment. When participants actively manipulated the orientation of an object (relative to passive viewing) during familiarization, their results indicated enhanced response accuracies and decreased reaction times in testing. This result accords with other studies of active versus passive adult learning within spatial environments (Péruch, Vercher, & Gauthier, 1995). Active and passive learning may differ with respect to the relative contributions of visual and proprioceptive feedback, attention, decision-making, and cognitive manipulation (Chrastil & Warren, 2012). The mechanisms facilitating adult visuospatial learning involve an active, volitional process called "spontaneous revisitation," entailing the active rescanning of items immediately after they have been viewed (Voss et al., 2011). This process may selectively enhance learning via recognition memory and spatial memory for object positioning. Active engagement with view manipulation has been shown to engage neural circuitry encompassing the left hippocampus, left medial prefrontal cortex, and right cerebellum (Voss et al., 2011). However, depending on the modality of sensory input, there may be multiple, integrated neural pathways by which learning occurs. Learning mechanisms may allow for integration of these inputs into higher-level, task-focused schema (Iran-Nejad, 1990).

The interactive nature of learning has been exemplified by experimental paradigms entailing both active and passive processing of stimuli. Wade and Holt (2005) devised a novel "space invaders" computer game task, where visually presented aliens preceded a complex sound waveform. The adult participants were not instructed to engage actively with or learn these sounds. However, discrimination of sound categories was beneficial to in-game performance. The authors found that postgame discrimination accuracy for complex sounds was positively correlated with in-game performance. Furthermore, conditions where sounds showed a reliable pattern produced better overall performance than conditions where sounds were

presented randomly. A subsequent fMRI investigation using the same paradigm revealed a significant correlation between changes in activation in speech-selective areas (left superior temporal sulcus) and behavioral accuracy in discriminating the passively encountered complex sounds (Leech, Holt, Devlin, & Dick, 2009). These findings suggest that for paradigms entailing some form of active engagement, learning may occur even when stimuli are encountered in an incidental fashion. Further, such learning might recruit neural regions specialized toward other cognitive or perceptual abilities, highlighting the potential for adaptation of cortical areas following active learning.

NEURAL UNDERPINNINGS OF LEARNING

Central to the learning mechanisms described above is the role of neural plasticity in allowing for experience to shape brain structure at both regional and circuitwide levels. A key scientific development in recent years has been the recognition of plasticity as a mechanism extending across the human life span. Developmental studies have reported increased myelination within subcortical white-matter tracts, including the left arcuate fasciculus and posterior corpus callosum, during childhood and adolescence. By contrast, grey-matter densities fluctuate during development, peaking in frontal and parietal regions at 10 to 12 years, before decreasing steadily into early adulthood (see Paus, 2005). Lövdén, Bäckman, Lindenberger, Schaefer, & Schmiedek (2010) argue that plastic changes in adult brain structure rely on a mismatch between the available functional capacity of brain networks and the cognitive demands placed upon those networks. Thus, a mismatch occurring within a network's range of potential performance may serve to spur neural plasticity, and hence facilitate learning (Lövdén et al., 2010).

Such mechanisms of plasticity can be considered from the perspective of second-language acquisition. The relative difficulty for adult learners in achieving nativelike proficiency in domains such as phonology is well documented (Birdsong, 2009; Ellis & Sagarra, 2011). Nevertheless, Birdsong (2009) highlights that adult second-language learners may display high proficiency within certain domains of language learning (e.g., syntax), compared to others (e.g., pronunciation; see also Flege et al., 1995). Lövdén and collaborators (2010) suggest that such disparities in language proficiency may reflect differences between the relative functional capacities of adult language networks and the functional pressures placed upon those networks. Thus, learning various facets of a second language (e.g., syntax versus pronunciation) may be driven by the existing capacity of a language network with respect to these facets, and the external, environmental pressures driving the network to master the facet most critical to the new language, in order to allow one to communicate effectively.

Neuronal plasticity may thus arise from differences in the capacities of networks to adapt to processing demands. The demands on functional neural networks will differ depending on the stage of learning. For example, recruitment of different neural circuits may occur at different stages of motor learning, and also at different times across development. Diamond (2000) notes that neocerebellar circuits are recruited most heavily during the early stages of motor learning, when task novelty is greatest. However, such neocerebellar circuits rarely achieve full development before early puberty, suggesting that their functional capacity in motor learning will differ both across development and across stages of learning (Diamond, 2000). The extent to which functional adaptation occurs within motor networks may also depend upon task demands. Reaching with a single hand when a force is applied to that hand produces a subsequent change in initial movement of the opposite hand; this pattern is not observed when a force is applied to one hand while reaching with both hands (Diedrichsen, 2007). This suggests that functional motor adaptation varies depending on the requirements of the task (i.e., functional pressure), and is based on the ability of the network to adapt following motor feedback, extending its functional capacity (Diedrichsen, 2007).

NOVELTY, MOTIVATION, AND LEARNING

The preceding accounts of adult language and motor learning highlight that mechanisms underlying plasticity and learning display a complex interaction with the functional capacity of neural networks. However, in considering *why* learning occurs, it is also important to recognize the relationship between learning and motivation. Researchers have long acknowledged the role of reward as a motivator of learning, acting to reinforce and increase the reselection of behaviors, based on coding of salient stimuli or events by the neurotransmitter dopamine (Dayan & Daw, 2008). However, recent neuroscientific investigations have questioned the role of reward, suggesting that rapidly occurring dopamine signals may facilitate learning depending on their occurrence with unexpected sensory events (Redgrave & Gurney, 2006). The novelty of events or stimuli may thus serve as a significant component accounting for motivation of behavior and learning (Bunzeck, Doeller, Dolan, & Duzel, 2012). Increased fMRI activation in the dopaminergic midbrain (substantia nigra/ventral tegmental area) in anticipation of novelty has been argued to display effects similar to the representation of reward cues, and may interact with activity in the hippocampal regions via dopaminergic input (Wittmann, Daw, Seymour, & Dolan, 2008). This loop of dopaminergic and hippocampal structures may form a motivational network with the medial prefrontal cortex, which can mediate representation of both novelty and reward. Such a system may further serve to motivate novelty-seeking, exploratory behaviors (Bunzeck et al., 2012). Thus, novelty may be a key factor underlying the motivation to learn, spurring pursuit of further novel stimuli or learning environments.

CONCLUSION

We have highlighted key changes in structural and functional neural organization over development, and have illustrated why brain-behavior links are likely to be bidirectional. We then have specifically addressed why learning in infancy

may involve active, experience-driven strategies, to ground our understanding of learning in a context-dependent manner. Our goal is to incorporate what we know about active learning in adulthood, and the neural changes that may be associated with this form of learning. The specific examples highlighted in this paper illustrate the complexity and dynamism of the human learning process. Inputs into learning can be influenced by the developmental processing occurring at the time of learning, prior expertise, and learning biases, as well as engagement with the activity in question, novelty, and motivation in general. Learning a given skill can therefore involve differential processing and demands, based on interactions among the factors outlined above. Therefore we have emphasized that, from a cognitive and developmental standpoint, our understanding of learning will be limited until we can ground it in a multifaceted framework, explaining the interplay of brain-behavior relationships along with the role of active participation in dynamic environments.

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Conflict of Interest Disclosure
The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. No conflicts were noted.

Author Contributions
The authors had equal roles in the writing of the manuscript.

Acknowledgments
This work was supported by grants to SK (Birkbeck College Research Scholarship) and DC (EC Marie Curie Fellowship PITN-GA-2010-256301 TRACKDEV). The authors would like to thank Professor Annette Karmiloff-Smith and Dr. Frederic Dick for their comments on early drafts of this article.

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What Do We Know about Spatial Navigation, and What Else Could Model-Based fMRI Tell Us?

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Spatial navigation, or the ability to remember and navigate environments, is an important skill for humans and animals. It has inspired a great deal of research, including neuroimaging studies of humans and single-unit recordings of animals. Recent advances in computational modeling have enabled spatial navigation in humans and animals to be investigated in a more precise and detailed manner. More specifically, computational models allow us to estimate theoretical parameters associated with spatial navigation, and model-based fMRI can be used to investigate the neural correlates of these parameters. This review addresses the literature on spatial navigation beginning with reviewing lesion and animal studies of spatial cognition. Imaging studies of spatial memory and navigation in humans, including structural imaging, and more-complex functional imaging studies involving virtual reality are then discussed. Particular emphasis is placed on computational studies of behavior involving reinforcement learning models and model-based fMRI. Finally, the advantages of model-based fMRI for investigating the neural basis of spatial navigation in humans are discussed.

INTRODUCTION

At one time or another we have each become lost—maybe in a new city, heading in the wrong direction or walking in circles on the way to the hotel. In contrast, most of us can travel to and from work each day without any problems, often arriving with little recollection of the journey we took and the decisions we made along the way. Remembering and navigating environments is of great importance for humans and animals alike, yet we often take it for granted. We tend not to appreciate our ability to navigate environments until we get lost in a new city, or when our ability to navigate is compromised by Alzheimer's disease (Henderson, Mack, & Williams, 1989) or other forms of dementia.

In this review I will discuss advances in the study of spatial navigation, including results from experiments in both animals and humans. Many methods have been used, including behavioral, neuropsychological, electrophysiological, neuroimaging, and computational modeling. I will introduce reinforcement learning, which is one aspect of theoretical neuroscience that has only recently been applied in studies of spatial navigation in humans and animals.

Navigation has been studied for a long time; it had many early breakthroughs, such as those of Tolman (1948), who interpreted both his own results (Tolman, Ritchie, & Kalish, 1946) and those of others (e.g., Blodgett, 1929) as evidence that a rat has an internal allocentric representation of space, or a cognitive map of its environment. Many of the major breakthroughs in our understanding of the neural representation of space—notably the discovery of place cells—have come from animals. These pyramidal cells in the rat hippocampus fire selectively in particular areas of the animal's environment (O'Keefe & Dostrovsky, 1971) and have been interpreted as a possible neural basis for Tolman's cognitive map (O'Keefe & Nadel, 1978), allowing the animal to navigate around obstacles or take shortcuts. More recently, head-direction cells, first found in the postsubiculum (Taube, Muller, & Ranck, 1990), and entorhinal grid cells (Hafting, Fyhn, Molden, Moser, & Moser, 2005), were discovered, the latter of which may form the basis of a path integration-based representation of the animal's environment. It is not completely clear how these findings relate to human navigation, although work has been done to find evidence for homologues of these cells in humans—for example, place cells (Ekstrom et al., 2003) and grid cells (Doeller, Barry, & Burgess, 2010).

SPATIAL MEMORY AND NAVIGATION

Neural Substrates of Spatial Memory

Since the case of patient H.M., who underwent a bilateral medial temporal lobectomy for intractable epilepsy, the medial temporal lobe (MTL), and the hippocampus in particular, have been associated with episodic memory (Scoville & Milner, 1957). In concordance with the discovery of place cells, and the idea of a cognitive map, the hippocampus is thought to be involved in spatial memory in animals (O'Keefe & Nadel, 1978; Morris, Garrud, Rawlins, & O'Keefe, 1982) and humans (Maguire, Burke, Phillips, & Staunton, 1996; Spiers, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2001). Hippocampal lesions have been shown to cause deficits in spatial memory in rodents (Morris et al., 1982), and electrical stimulation of the entorhinal cortex, an MTL structure associated with the hippocampus, and its main interface with the neocortex, has been linked to improved spatial memory in mice, possibly related to improved adult neurogenesis in the dentate gyrus (Stone et al., 2011).

In humans, many different methods have been employed to discover the exact relation of the hippocampus and other brain structures with spatial memory and navigation.

A voxel-based morphometry study showed structural differences between licensed London taxi drivers, who must pass a rigorous test of their knowledge of London roads (and thus are expected to have better spatial memory), and controls (Maguire et al., 2000). It was found that the taxi drivers had larger posterior hippocampi and smaller anterior hippocampi compared with controls. This change in hippocampal size was also found to correlate linearly with the number of years of experience the taxi driver had (Maguire, Woollett, & Spiers, 2006). In concordance with rodent-study results, electrical stimulation of the entorhinal cortex in epileptic patients undergoing invasive recordings prior to surgery resulted in quicker and more-accurate navigation in a simulated environment (Suthana et al., 2012). It is tempting therefore perhaps to link these two studies with the rodent study connecting adult neurogenesis with improved spatial memory to suggest that increased adult neurogenesis in the dentate gyrus results in a greater number of hippocampal cells, underpinning the remarkable talents of the London taxi drivers. This possible mechanism for acquisition of spatial memories has much support; adult-generated dentate gyrus cells are preferentially recruited into neural networks associated with spatial memories (Kee, Teixeira, Wang, & Frankland, 2007), and many models have been proposed to link adult neurogenesis with hippocampal learning (e.g., Becker, 2005; Aimone, Wiles, & Gage, 2006). However appealing this theory may be, there has been no conclusive supporting evidence for it.

None of the studies mentioned provides any insight into how humans or animals use these structures to know where they are and how to navigate to a goal location. Place cells are clearly an important element of spatial cognition and navigation, but there is a limit to what we can find out using experimental animals. Single-unit recordings in freely moving animals produce sensory-motor confounds; these can be controlled better by using human subjects, who are also assumed to be better at navigating and making decisions within their environments. However, one issue when studying navigation is the scale of the problem; naturally, humans navigate in large-scale environments, something that is difficult to reproduce in a controlled laboratory setting. Traditional tabletop tests of spatial memory do not accurately test natural navigation (Maguire et al., 1996), as the subjects are required to solve the problems from different viewpoints or in different reference frames from the ones they would naturally employ. Natural navigation tasks are more realistic, but they present problems when the researchers are trying to control between subjects, or accurately record performance spatially and temporally. One solution is to use virtual reality (VR).

Functional Imaging of Navigation

One of the major advantages of VR is the possibility of combining it with other techniques; its nature allows the subject to explore a virtual environment on a screen, while remaining still enough to allow functional images or single-cell recordings to be taken. Some early VR studies of spatial memory (e.g., Aguirre, Detre, Alsop, & D'Esposito, 1996) showed activation in certain brain areas (parahippocampus and associated cortex). However, it is difficult to break down the activation patterns of these studies to find the particular activity underpinning the task. Further studies have illuminated the function of different areas during navigation, using, for example, positron emission tomography (PET) while participants navigated a complex but previously experienced VR town (Maguire et al., 1998). The subjects underwent four different navigation tasks, allowing the authors to find that the participants' speed moving through the environment was associated with caudate activation, activity in the right hippocampus was associated with navigation accuracy, and activity in the left hippocampus was associated with navigation success. Bilateral medial and right inferior parietal activation corresponded with movement through the environment, and prefrontal activation was associated with success in navigating around blocked routes. However, due to the technique used (PET), between-subject effects could not be distinguished.

Recently, the use of PET has decreased in favor of functional magnetic resonance imaging (fMRI), which has many advantages, such as higher temporal resolution and very high spatial resolution. Using fMRI, Hartley, Maguire, Spiers, and Burgess (2003) expanded on the PET experiments, finding that in successful navigators, anterior hippocampal activation was correlated with way-finding, and caudate activation was correlated with route following (hence the correlation with speed found in Maguire et al., 1998).

As well as finding which brain areas are active during navigation, more-recent experiments have sought to determine which aspects of navigating in a virtual environment correspond to the detected activity. Correlations between hippocampal activity and navigation relying on spatial memory of the environment, and between parahippocampal activity and navigation relying on contextual memory (that is, the relationships between landmarks—"the post office is to the left of the statue"), have been found using variants of a learned environment (Rauchs et al., 2008). Functional segregation of the MTL at different phases of navigation has been investigated by testing subjects in variants of a learned VR environment (Xu, Evensmoen, Lehn, Pintzka, & Håberg, 2010). The authors found that anterior MTL (anterior hippocampus, entorhinal cortex, and anterior parahippocampal cortex) was active only during the initial phase of navigation, involving self-localization and planning routes (as reported by the participants), and the posterior MTL (posterior hippocampal and posterior parahippocampal cortex) was active throughout navigation, presumably corresponding to processing spatial information relating to the subjects' current position within the environment.

Using a similar but much more detailed method than Xu et al. (2010), Spiers and Maguire (2006) sought to investigate the neural activity corresponding to more-detailed aspects of navigation as their subjects (taxi drivers) drove around London in response to requests from customers. After the subjects finished the task and left the scanner, they were

immediately shown a replay of their navigation, and were interviewed to discover what they were thinking at different stages of the navigation. The verbal report protocol used with the subjects following the scan allowed the authors to break down the task into many more subcomponents than previous studies had, including visual inspection, action planning, and simply coasting. The authors found that, during the initial planning of the route, there was activation in the whole spatial-navigation network, including the hippocampus, as well as activation in lateral and medial prefrontal areas. When subjects altered their route during the journey, activation was seen in retrosplenial and right parietal cortices as well as prefrontal areas. The subjects interviewed reported expecting particular routes or landmarks; when these expectations were fulfilled, the retrosplenial and posterior parietal cortices were active. However, if, for example, they encountered a blocked route, the right lateral prefrontal cortex became active, supporting previous studies linking this area to detecting violations of expectations (e.g., Corlett et al., 2004).

These studies provide an insight into how the brain keeps track of our position as we move through space, but we do not know as much about how we navigate toward a goal location. Studies such as Spiers and Maguire (2007) provide evidence for internal metrics of goal location and distance, supporting models (e.g., Burgess, Jackson, Hartley, & O'Keefe, 2000) of how organisms navigate to a goal. This does not, however, provide any evidence for how the brain makes decisions during navigation, particularly at vital points such as when the route is blocked. Computational models have been developed to explain how organisms make decisions, and by combining these with functional imaging techniques, it is possible to discover how decision processes are carried out in different regions of the brain during navigation. These models, and their implementation along with functional imaging, will be discussed at greater length below.

As sophisticated as fMRI techniques have become, they are particularly limited by their temporal resolution. As such, more-direct measures of neural activity, such as electroencephalography (EEG) and magnetoencephalography (MEG), have been used to study the association between navigation and high-frequency brain activity, such as the theta rhythm. The theta rhythm has been linked to spatial behavior in rodents, and there is evidence from EEG (Kahana, Sekuler, Caplan, Kirschen, & Madsen, 1999) and MEG (de Araújo, Baffa, & Wakai, 2002) that these theta oscillations are linked to navigation in humans as well as lower mammals. More recently, MEG has been used to determine the function of these theta oscillations in human navigation. Cornwell, Johnson, Holroyd, Carver, and Grillon (2008) used a virtual Morris water maze and found that anterior hippocampal theta was implicated in the encoding of the spatial environment, and posterior hippocampal theta was highly correlated with navigation performance.

There is now good evidence for the neural basis of Tolman's (1948) cognitive map, with location-specific hippocampal cells observed, and structural changes in the human hippocampus that correlate with spatial-memory abilities. However, because of the very nature of the problem, navigation in humans is hard to test, and this has led to the development of VR environments to investigate navigation in a controlled manner. VR has been successfully combined with functional imaging, and the hippocampus has been consistently linked with navigation accuracy, particularly in the early stages of navigation, in which recall of memory is most vital. Electromagnetic methods (EEG and MEG) have also been used, and a link made between the hippocampal theta rhythm and navigation. These results show that the hippocampus is almost certainly responsible for spatial cognition in animals and humans, but there is still much to be discovered. Less is known about how we make decisions during navigation, but this is where computational models may help us answer these questions.

COMPUTATIONAL MODELS

Neural systems have also been extensively modeled computationally; these include place cells (Sharp, 1991; Hartley, Burgess, Lever, Cacucci, & O'Keefe, 2000) and rat navigation (Brown & Sharp, 1995; Burgess, Donnett, Jeffery, & O'Keefe, 1997). The class of models on which I will focus will be those of reinforcement learning (RL) (Sutton & Barto, 1998), which have been used in model-based fMRI studies. RL formalizes the "law of effect" (Thorndike, 1911), which states that actions that lead to positive outcomes are more likely to be repeated. While RL models vary, they all seek to learn the value of a stimulus or action that in some way represents the reward associated with that stimulus or action. Rescorla and Wagner (1972) sought to apply this idea to classical conditioning, and devised a formula to calculate the associative strength of a conditioned stimulus after a reward. Their updated rule was interpreted as a prediction error (between the reward expected and that obtained), and was advanced by the development of a real-time, trial-by-trial temporal difference (TD) error (Sutton & Barto, 1990). The simplest TD algorithm updates the value Vst of a state, s at time, t as $V_{\downarrow}st$ ($V_{\downarrow}st + \alpha[r_{\downarrow}(t + 1) + \gamma V_{\downarrow}(st + 1) - V_{\downarrow}st]$ (Sutton & Barto, 1998), using the observed reward (r_{t+1}), a learning rate between 0 and 1 (α), and a delay discount (γ) between 0 and 1, so that delayed rewards have lower importance than immediate ones. The agent then uses these calculated values to make a decision when required, employing, for example, the softmax activation function, which converts the value of a state into a probability of action using a temperature parameter, determining the stochastic nature of the choice. This action then determines the next state the agent experiences and the reward received from the environment, and the value of the new state is then updated. These model parameters can be determined by various means, which will be discussed in the context of the application of these models to fMRI.

Neural Basis of Reinforcement Learning

It has been shown that RL algorithms can provide a good

estimation of neural activity in both animals and humans. Theories have been proposed that credit the action of the dopaminergic system and its inputs to the striatum with implementing the RL prediction error (Schultz et al., 1995); these theories are supported by single-unit recordings in monkeys (Schultz, Dayan, & Montague, 1997). Similar results were found in an fMRI experiment involving humans and a simple operant conditioning paradigm (Pagnoni, Zink, Montague, & Berns, 2002). The authors found a pattern of activity in the ventral striatum (innervated by the dopaminergic system) that showed differentiation between trials with an expected positive stimulus, and those when the stimulus was withheld. Patients with Parkinson's disease (in which striatal dopamine levels drop) have also shown difficulties when learning from feedback (Knowlton, Mangels, & Squire, 1996; Shohamy et al., 2004). These studies, however, do not fully explain what the dopamine signal represents, as it has been shown that it may represent motivation, an incentive salience, rather than an RL prediction error (Flagel et al., 2011). Despite this uncertainty, RL algorithms have been widely applied, including in the fields of spatial cognition and navigation (Foster, Morris, & Dayan, 2000; Sheynikhovich & Arleo, 2010; Gustafson & Daw, 2011).

MODEL-BASED fMRI

Model-based fMRI is a recently developed technique with the potential to uncover much more detail about how the brain carries out complex processes. All imaging-analysis methods could be considered model-based methods, in that they rely on assumptions or models of how the brain functions. Model-based fMRI, however, is a specific technique that involves using computational models to analyze how fMRI signal changes correlate with quantitative computational predictions of neural activity, rather than simply stimulus inputs and behavioral responses. This technique allows hidden variables and computational processes to be uncovered in ways not possible with traditional event-related or parametric paradigm designs**.** In most of the studies mentioned above, the activity reported is averaged across many trials, but by using computational models, fMRI can show not just which brain area's activity is correlated with a task but also how that brain area may carry out the task, on a trial-by-trial basis. The internal variables, such as prediction errors and state-values of RL models, calculated at each time step can be used to test different hypotheses about the possible ways the brain implements learning from reward and punishment.

Choice of Parameters

One of the main problems in the development of the RL model is that of choosing appropriate model parameters. Each of the parameters, such as the learning rate and the softmax temperature, must be chosen separately. An attractive but potentially problematic method is simply to choose parameters based on the experimental literature. However, free parameters can vary greatly among different subjects and different experimental paradigms (Kim, Shimojo, & O'Doherty, 2006; Wittmann, Daw, Seymour, & Dolan, 2008; Daw, Gershman, Seymour, Dayan, & Dolan, 2011; Li & Daw, 2011). A popular method for estimating the free parameters is that of maximum likelihood. Optimization algorithms are available that iteratively adjust parameters to minimize the difference between the choices predicted by the model and those actually made by the subjects during the task to find the most likely parameter combinations. These algorithms are conceptually simple but are of limited use in complicated parameter spaces. Other methods (e.g., Bayesian) are conceptually more difficult and more computationally intensive, but may offer a better estimate of the parameters, and hence a better model. Once chosen, the parameters can then be used with the RL model to generate the internal variables at particular time points of the experimental task. The time series' variables are then convolved with the canonical hemodynamic function to allow for the delay between neural activity and the hemodynamic response of the neural tissue.

Hypothesis Testing-Model Comparison

As is standard in fMRI experiments, the model-predicted time series is used as a regressor against the fMRI data in a general linear model (GLM) (Friston et al., 1995). The GLM allows areas of the brain to be found where the changes in the BOLD signal have a statistically significant correlation with the model-based time series. In decision-making experiments, and fMRI experiments in general, simply finding correlated activity in a brain area doesn't show how the associated computations of the chosen model are carried out in that area. Another approach is that of model comparison, to test hypotheses of how the brain areas carry out the necessary computations for the task. Different candidate models or hypotheses may be compared to determine which model best explains the data. Often the models compared will be simple variations; in the case of RL, this could be between an on-policy TD algorithm such as SARSA (Rummery & Niranjan, 1994) or an off-policy algorithm such as Q-Learning (Watkins, 1989). Another possibility is to compare how computations are implemented more fundamentally, such as comparing model-based and model-free TD learning (Daw, Niv, & Dayan, 2005; Simon & Daw, 2011).

Simply comparing how well the different models fit the behavioral data at the maximum likelihood parameter estimates could constitute model comparison. However, this does not provide a useful answer because generally, model fit is dependent on the number of free parameters; the more free parameters there are, the better the fit. A more complex model is not necessarily better; it may just fit better to noise in the original data, and provide a worse fit to a second data set. Because of this, there are various model-comparison techniques available, such as the likelihood ratio test (Mood, Graybill, & Boes, 1974) or cross-validation (Bishop, 2006), which involves fitting the models to a subset of the data, then testing the models on the full data set. However, this method is rarely used in RL because it is difficult to split time-series data into two independent subsets (Daw, 2011). Another way of approaching model comparison is to use Bayesian methods, such as calculating

the ratio of the model evidences, known as the Bayes factor (Kass & Rafferty, 1995).

There are many methods available to compare models, but one can never be sure that the chosen model is the best available, or that a superior model will not be formulated at a later date. For this reason, a hypothesis test must be carried out to calculate the evidence in support of the null hypothesis, and whether or not it can be rejected in favor of the alternative hypothesis (the particular model to be tested).

MODEL-BASED fMRI STUDIES OF LEARNING AND DECISION MAKING

Previous fMRI studies (e.g., Pagnoni et al., 2002) found BOLD responses consistent with the prediction error (PE) in temporal-difference RL when an outcome was unexpected, but did not seek to discover whether neural activity corresponded with the predictions made by the TD algorithm throughout different stages of learning. O'Doherty, Dayan, Friston, Critchley, and Dolan (2003) used fMRI while participants took part in a Pavlovian conditioning task, and sought the neural correlates of the TD prediction error at different time points of the conditioning before, during, and after learning. The authors found activity in the ventral striatum and orbitofrontal cortex (OFC), which correlated significantly with the model-derived PE signal.

In addition to the prediction error between the reward expected and that received, it has been hypothesized that the brain might keep track of estimated rewards if previous decisions had been made differently. This would allow a distinct fictive error signal, which would further aid the organism in making future decisions. A neural correlate of this signal in the ventral caudate was found that served to modulate the behavior of subjects while they took part in an investment game (Lohrenz, McCabe, Camerer, & Montague, 2007).

A potential problem with RL is that when someone is simply learning values associated with states or actions, the higher-order structure of many tasks or environments cannot be used to make decisions. This was investigated by comparing a simple RL algorithm with a more complex computational model that incorporates the higher structure of a task carried out by participants: probabilistic reversal learning (Hampton, Bossaerts, & O'Doherty, 2006). Activity in the ventromedial prefrontal cortex (vmPFC, a region previously associated with decision making) correlated with the probability of the correct action being chosen, derived from the more complex model incorporating the structure of the task. This result is consistent with fMRI studies showing that model-generated expected-value signals associated with a stimulus are correlated with the BOLD response in various frontal cortical regions, including the vmPFC (e.g., Kim et al., 2006).

There is some uncertainty about whether the dopamine signal in the brain represents a prediction error, but there appears to be a good concordance between RL models and neural activity in experimental animals and human subjects. These models have more recently been used to analyze fMRI data in a more detailed manner, to investigate where in the brain particular elements of a calculation are represented. This technique has provided insights into the neural basis of learning and decision making, such as the finding that activity in the ventral striatum and OFC correlate with the RL prediction error. However, until recently this has been restricted to decision making in non spatial tasks.

APPLICATION OF MODEL-BASED FMRI TO SPATIAL NAVIGATION

Since the time of the early cognitive map work, a distinction has been made between different types of spatial behavior. Blodgett and McCutchan (1947) discussed the difference between "place" and "response" learning. The former could be explained by the spatial memory encoded by place cells, and the latter could represent a simpler form of navigation, one that relied on making decisions at certain points without necessarily keeping the goal location in mind. This could well be explained by the theory of RL, and is the basis for applying model-based fMRI (using RL algorithms) to spatial navigation. Model-based fMRI has previously been applied to studies of learning and decision making; however, one study (Simon & Daw, 2011) was the first to combine model-based fMRI and VR to understand spatial navigation. Different models of how the subjects could navigate around the environment were compared—particularly whether the subjects' behavior could best be explained by a model-based RL algorithm in which the subjects used their knowledge of the structure of the environment, or by a simpler TD algorithm. In their experiment, subjects navigated in a simple 4x4 grid, with the aim of navigating toward goal locations corresponding to a monetary reward. Various models were tested, and it was found that the model-based RL algorithms fit the behavioral data much better than TD, indicating that subjects plan ahead, using a spatial map of the environment. A concurrent fMRI scan found BOLD signals within the striatum that correlated with both choice and value-related variables from the model-based RL algorithm. This is in contrast to the traditional view of the striatum being responsible for habit learning and route following. Other model-based parameters (correlated with value) were found to be correlated with activity in the medial temporal lobe and frontal cortex, concordant with previous theories about the neural basis of forward planning and internal representations of space.

This study is interesting as the first application of model-based fMRI to spatial navigation, and it begins to answer some important questions in the field. The results hint at whether people use an internal map of their environment, planning potential routes, or whether they simply follow the same paths to goals. This method could also be used to try to distinguish how the brain encodes the distance to the goal. Although it is known that the hippocampus is necessary for encoding spatial relationships, it is not known for certain whether its activity represents distance to the goal

in a Euclidian way (as the crow flies) or whether it represents the path distance, taking into account shortcuts or the distance around obstacles. Recent evidence, however, has shown that anterior hippocampal activity correlates with the Euclidian distance to the goal, and posterior hippocampal activity is linked to the path distance; which is active depends on the stage of navigation (en route, at decision points, etc.) (Howard et al., 2011). That the brain represents both Euclidian and path distance is unsurprising, as both are likely to be needed for accurate navigation in large-scale, complex environments. The value of the goal and the cost of travel are also likely to be as important as, if not more important than, the distance to be traveled when calculating paths and making decisions; model-based fMRI may provide explanations of how these variables interact in the brain.

The Simon and Daw study (2011) is a promising starting point for the method, although future studies need to be carried out to answer many of the unresolved questions within spatial navigation. The study used a highly artificial environment that, although it allows for a simple analysis, does not allow natural navigation to be investigated. To further elucidate the neural basis of decision making during navigation, a more complex, more natural environment could be used, whether with a VR environment (e.g., Hartley et al., 2003) or video recordings of natural scenes (e.g., Howard et al., 2011). Although the environment was designed to encourage a model-based strategy by incorporating dynamic rearrangement of the doors between the rooms, the subjects were always able to see the goal location above the other rooms. This makes it possible that in some of the trials, the subjects were simply trying to move closer to the goal and not thinking about the structure of the environment. If, in another experiment, the subjects were taught the environment and the goal locations prior to scanning, but then could not see them directly, they might be more likely to plan routes ahead and navigate in a more realistic manner.

LIMITATIONS OF MODEL-BASED fMRI

Although model-based fMRI is potentially a powerful technique, and has great promise in the field of spatial navigation, it is not without its limitations. Model-based fMRI is intrinsicly limited by the imaging technique itself. Unlike single-unit recordings in animals, fMRI is an indirect measure of neural activity, and has low spatial and temporal resolution. As such, it can provide only an estimate of the average firing of neurons in a brain region, not the patterns of activity of individual neurons. To determine more precisely how (if at all) these algorithms are implemented in the brain, other techniques such as single-unit recordings or more-direct measures of neural activity in humans may be required, such as EEG or MEG, which could be used to uncover more accurately the time course of the activity. Another fundamental limitation of fMRI is that only a correlative, not a causal, link can be established between the neural activity and the subjects' behavior. To determine whether the region is necessary for a particular task, it must be disrupted, either by a preexisting lesion or by the use of transcranial magnetic stimulation (Barker, Jalinous, & Freeston, 1985). As both navigation and decision making are complex processes, it is unlikely that the processes necessary for these tasks are carried out in individual brain areas. It is more likely that the computation is carried out as a dynamic pattern of activity and flow of information through many different brain areas. This is difficult to detect using simple model-based fMRI, although work has been undertaken to uncover interactions between different brain areas using techniques such as dynamic causal modeling (Friston, Harrison, & Penny, 2003). Model-based fMRI also has its own disadvantages compared to traditional fMRI, as it involves finding brain areas where the activity correlates with variables predicted by a particular model. This approach can prevent the discovery of results not expected a priori, and for this reason it is probably wise to carry out a conventional trial-based analysis of the fMRI data in conjunction with the model-based approach.

Rather than just using model-based fMRI or comparing results with other techniques, a similar model-based analysis could be applied to any physiological measure that correlates with behavior. RL models could be adapted to carry out model-based analyses of imaging data from other, complementary techniques such as EEG/MEG or measures such as eye tracking. These methods could be formally combined—for example, simultaneous EEG-fMRI recording (see Laufs, Daunizeau, Carmichael, & Kleinschmidt [2008] for a review)—to potentially provide an insight into the computational processes carried out by the brain during navigation at a high spatial and temporal resolution.

The most important limitation of any model-based analysis is the assumptions it requires. Model-based fMRI requires many steps, from constructing the models and designing the experiment to collecting and analyzing the data. In all this it is easy to forget that the whole technique relies on an assumption that the brain reduces a very complicated problem to a few simple steps with particular variables. It is important to remember that this may be a flawed construct, and just because the analysis gives an appealing answer, that does not mean it is necessarily true. Any evidence this method provides must be interpreted in the light of the rest of the experimental literature, and supported by results obtained by other methods.

The application of model-based fMRI to spatial navigation research is promising, although only one study has yet been performed (which was designed to study decision making in a navigation paradigm, rather than navigation itself). This method has the potential, however, to reveal how humans use internal models of their environment, how they assign value to parts of their environment, and how they use this information to make decisions and navigate accurately. But to accomplish this, care must be taken to design tasks that will allow these variables to be investigated, while ensuring that the navigation paradigm corresponds well to real-world tasks. Model-based fMRI has many limitations, most

of which are simply the limitations of the imaging modality itself; they can be overcome, at least in part, by combining or comparing results from model-based fMRI with results from other methods. However, model-based fMRI rests entirely on the validity of the models chosen for the analysis, and this must be kept in mind when one is interpreting results.

CONCLUSION

Much has been learned about spatial memory, from single-unit recordings in animals to sophisticated imaging studies in humans. RL algorithms have helped our understanding of how we and other animals learn about our environment and make decisions. The application of these models in model-based fMRI results in a particularly powerful technique, allowing researchers to detect where in the brain specific elements of particular computations are carried out. The study by Simon and Daw (2011) is a promising starting point for the application of the method to spatial navigation; however, as the authors acknowledge, their study was more like others designed to investigate decision making rather than spatial navigation. To investigate the unanswered questions in navigation, such as how we make decisions and use models of our environment, the method needs to be improved, advanced, and perhaps supplemented with model-based analyses of other techniques, such as EEG/MEG.

Because model-based fMRI relies on the validity of applying RL models to spatial navigation, this must also be investigated. Experiments in animals may provide a method for doing just this. Selective inactivation, both in time and space, of areas thought to be involved in RL-related processes as an animal learns and navigates within an environment could be used to investigate the validity of applying models originally developed to explain learning in conditioning paradigms to spatial navigation by humans in complex environments.

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Conflict of Interest Disclosure

The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. No conflicts were noted.

Acknowledgments

The author thanks Dr. Hugo Spiers for his helpful suggestions in the writing of this article.

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The Use of Personal Accounts in the Study of Severe Mental Illness

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This paper looks at the use of personal accounts in the education of medical students in psychiatry. It discusses the practice of giving students protected reading time to review case material that will prepare them for future clinical interactions. Much can be learned from personal accounts of severe mental illness that cannot be gleaned from shorter case studies. This paper discusses how personal accounts can uniquely shed light on the following aspects of a patient's subjective experience: breaks with reality, loss of sense of self, social isolation, the therapeutic relationship, stigma, coping, and recovery. Using such narratives as a foundation, students can internalize a broader portrait of psychiatric patients, of their capacity for change, and of the discipline of psychiatry itself. This broader picture is useful because medical students' exposure to psychiatry is typically narrow, focusing largely on interaction with patients at their worst, when they require hospitalization. The narrow exposure in turn conveys a myopic picture of the individual patient experience and of the field of psychiatry as a whole. The use of personal accounts in the study of mental illness can counter this effect.

INTRODUCTION

The current Liaison Committee on Medical Education (LCME) accreditation standards require medical schools to "establish a system to specify the types of patients or clinical conditions that medical students must encounter" and to monitor their experiences. If a medical student does not encounter certain types of conditions, the training director can remedy the deficiency with a standardized patient experience: an online or paper case (Liaison Committee on Medical Education, 2013).

On psychiatry clerkships at Albert Einstein College of Medicine, students are given a list of required cases at the beginning of the rotation and paper cases are used to fill in deficiencies. In general, the paper cases are taken from standard texts, such as the casebook for the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) (Spitzer, Gibbon, Skodol, Williams, & First, 2002) and its treatment companion (Spitzer, First, Gibbon, & Williams, 2004). These cases are derived from clinical practice and are useful for teaching differential diagnosis and the diagnostic criteria outlined in the DSM-IV-TR (American Psychiatric Association, 2000) and the recently released DSM-5 (American Psychiatric Association 2013). They contain a psychiatric history and mental status features but often don't reveal the subjective experience of the patient, the fluidity of that experience, and the potential for change. Their intention is to portray symptomatology, not ego strengths and features of psychological health. The focus is not on coping strategies for living with mental illness, social support systems, or recovery.

Problem-based learning (PBL) cases are equally useful for teaching psychiatry (Guerrero & Piasecki, 2008). PBL is an active, student-centered form of learning in a group setting. Written cases are used to help students problem-solve with faculty facilitation. Ideally, a PBL case recreates a patient narrative (MacLeod, 2011) and teaches "patient-centered care" (Bauman, Fardy, & Harris, 2003) by centering the patient and the illness within a social context. However, rarely does a PBL case contain the patient's own words, and in one study of PBL cases the inclusion of social factors was limited (MacLeod, 2011).

We would argue that the use of personal accounts in teaching is one way to provide the social context that is missing from some DSM and PBL cases. Personal accounts are written in the patient's own words and allow "glimpses into the subjective world of lived experience" (Kumagai, 2008).
The patient's subjective experience has long been a concern of psychiatrists, as Strauss and Estroff (1989) noted two decades ago: "Patients' reports of their experiences have been the data base for descriptive psychiatry from the time of Kraepelin and Jaspers to DSM . . . and no doubt will continue to serve that role" (p. 177). More recently, Roberts (2000) has made a forceful argument for the role of patient narratives in an evidence-based world.

At least two psychiatry journals, *Schizophrenia Bulletin* and *Psychiatric Services,* continue to publish first-person and family accounts. Other mental-health professionals publish personal accounts in their journals (Frese, 2000) and as texts (Sattler, Shabatay, & Kramer, 1998; LeCroy & Holschuh, 2012), and personal accounts are also published as memoirs (Saks, 2007; Cockburn & Cockburn, 2011). These accounts reach a wide audience of patients, clients, and clinicians, and enable readers to better understand the illness experience and the process of recovery. They uniquely portray the loss of sense of self that occurs with severe mental illness; regaining or managing that loss can lead to recovery (Wisdom, Bruce, Saedi, Weis, & Green, 2008). They demonstrate the powerful role of the family and social factors in the recovery of the lost self.

Table 1 | Sample Trigger Questions

Questions
What is the narrator experiencing?
What reactions/emotions did the account evoke in you?
What can you do to prepare for an interview with this person?
Do you see evidence of distorted reality? Other symptoms of schizophrenia?
Describe the role of the therapeutic alliance in severe mental illness.
What role does stigma play in mental illness?
What do we mean by "early warning signs"? How are they helpful?
What are some coping strategies used by people with severe mental illness?
What are signs of recovery?

WHY READ PERSONAL ACCOUNTS OF SEVERE MENTAL ILLNESS?

Medical students in the third-year psychiatry clerkship have been taught the DSM-IV definition of schizophrenia: a serious disorder with a minimum of six months of certain symptoms. For at least one month, the patient has two or more of the active-phase symptoms: delusions; hallucinations; disorganized speech, behavior, or both; and negative symptoms. The patient may experience prodromal or residual symptoms—negative symptoms or attenuated active-phase symptoms—within the six-month period. The patient's social and occupational functioning is impaired (American Psychiatric Association, 2000).

Over time, these symptoms alter "the most basic functions that give the normal person a feeling of individuality, uniqueness, and self-direction" (Sadock & Sadock, 2005). The illness shatters multiple aspects of the self and can feel strange and incomprehensible to a medical student who encounters it for the first time. The patient with schizophrenia loses touch with reality as the student knows it, and the symptoms appear to replace the personality of the individual. The symptoms of paranoia and aggression can induce fear in the student, and the extreme isolation of the patient can be daunting for a beginning interviewer. There are also countertransference feelings to contend with: for example, the student may bring along stigmatizing attitudes from the larger culture (Rüsch, Angermeyer, & Corrigan, 2005).

The reading of personal accounts during the psychiatry clerkship can not only teach symptoms and diagnostic criteria but enable the student to gain some mastery over his or her preconceptions and emotional reactions.

THE ACTIVITY OF READING FOR MEDICAL STUDENTS

It is important to understand the activity of reading narratives from the medical student's perspective. A medical student, when meeting a patient for the first time, can experience distractions that make it difficult to concentrate attention on the patient. There is the distraction of trying to recall all the questions students must learn to ask, concern about the supervisor's assessments and grades, and anxiety about interacting with certain types of patients, who may be uncooperative, angry, or dismissive. There are also the distractions of the interview setting, such as those found in a noisy and crowded emergency room or on the psychiatric inpatient ward. Ultimately, it is essential to learn to tolerate and manage these kinds of distractions. However, a student can more easily adjust to and develop skills for the interview experience by reading beforehand.

For a medical student, reading a narrative account of an individual's experience of illness can provide a quiet and protected space without any of the aforementioned distractions, a space in which the student can focus entirely on the

Table 2 | Learning from Narratives

Narrative	Learning Objectives
"Henry's Demons" (Cockburn)	Loss of touch with reality Ideas of influence Hallucinations Role of family and friends in treatment compliance
"Who Are 'They'?" (Wilson)	Paranoia Ideas/delusions of reference Delusional system Loss of sense of self
"Schizophrenia and Socialization" (Fox)	Racing, intense thoughts Poor judgment Loss of social supports Resocialization
"More Magic Bullets?" (Neugeboren) "The Center Cannot Hold: My Journey through Madness" (Saks)	Importance of the therapeutic relationship
"First-Person Account: Landing a Mars Lander" (Parker) "Schizophrenia" (Ben-Dor)	The role of stigma in mental illness
"How I Perceive and Manage My Illness" (Leete)	Early warning signs Coping strategies
"Recovery as Discovery" (Scotti)	Signs of recovery

individual's experience of illness. The act of reading itself, and the relationship the reader develops in his or her mind with the narrator, can serve as a model for the kind of intellectual and emotional engagement that doctors develop with their patients. In the words of one eloquent academician, when students read fiction or nonfiction narratives of illness, "it allows them the possibility to step out of the professional space and meet the persona in his crisis" (Kleppe, 2006). The reader can concentrate exclusively on the narrator's experience and attend to whatever emotions that experience induces. It is important to do this prior to meeting the patient. Once the student enters the clinical setting, he or she will have to maintain proper personal boundaries and engage the analytical, non-emotional part of the mind in deriving the differential diagnosis and treatment plan.

If the student/reader experiences emotional reactions to a patient's raw emotions on the written page, he or she has a protected setting in which to deal with those emotions. "Protected reading" in a protected setting allows for increased reflection, as do follow-up discussions with the psychiatry instructor and other students. Examination of the affective or emotional domains is one of Epstein's steps in developing mindfulness or "mindful practice" (Epstein, 1999).

LEARNING FROM PERSONAL ACCOUNTS

On the psychiatry clerkship, excerpts from personal accounts can be given as class readings prior to meeting with patients with severe mental illness. The instructor summarizes the book or article and frames the context prior to introducing the reading. Some examples are excerpted below. They have been shortened for the purposes of this article, but the attached references will give the instructor and reader access to the full accounts.

These examples were culled from what is available in the literature: from *Schizophrenia Bulletin* and *Psychiatric Services,* which include articles written by members of the psychiatric consumer movement, and from memoirs. Personal accounts are not always available to demonstrate every symptom of schizophrenia. The goal is to present the student reader with the illness experience so the patient's story can reinforce the memory of the symptom (Roberts, 2000), coping skill, or sign of recovery, and the reading of the narrative can prepare the student to meet the patient. Using sample trigger questions (Table 1), faculty members can review observations from individual narratives (Table 2).

The Break with Reality

In a book-length memoir, *Henry's Demons*, a father and son give their individual perspectives on the son's illness (Cockburn & Cockburn, 2011). Henry, the elder of two sons, had his first psychotic break at the age of 20, during his first year of college in England. The book was written seven years later, after seven hospitalizations, when Henry was an outpatient.

At the time of his first psychotic break, his mother and brother visit him at college. Henry writes about the visit:

> My brother, Alex, was coming down to Brighton to see me. I wanted to make a drum for him. I left college in search of clay for it. . . . I found myself walking on a road parallel to the train tracks. I felt I was going on a mission. . . . I sat under a big tree. . . . I felt the tree telling me to take off my shoes. I was scared, as I had been arrested previously for not wearing shoes. . . . A dog barked, and I held my breath for as long as I could until I soiled myself. I saw flashlights and people looking for me beside the railway track. The root of the tree moved as it touched me. . . . After talking to the tree, I had thrown away the pieces of wood and tin. . . . Everything seemed to want me to leave Brighton, but my brother was coming down for the weekend, and I felt I couldn't abandon him. . . . When I got back, my mother was furious with me for being three hours late. Eventually, she calmed down and let Alex spend the night with me. (pp. 39–41)

To the student/reader, the rhythm of the narrative sounds odd. The events occurring in his mind (such as the tree talking to him) and the events occurring externally (such as meeting with his mother and brother when they visit him in Brighton) are equally real to him and are woven seamlessly into one narrative. This juxtaposition reminds the reader how disorienting, difficult, and exhausting it is to be living in two parallel realities.

The Experience of Paranoia and Loss of Self

In her first-person account "Who Are 'They?'" Molly Wilson (2007) describes her paranoia and fears of others. She gives a vivid picture of her loss of sense of self as a result of being in "a terrible game."

> Communications were totally confused. I thought conversations were all about me disguised only by different names people used. So if people hated someone or thought someone wasn't nice, they were really talking about me. I believed that the radio in my car was tapped and that the announcers were talking about me. I also thought movies were en-coded to send a message about what they thought of me. . . . I lost my opinions. I forgot who I was and what I believed in. I thought I was in a terrible game, a game where I was the victim and everyone else were players. (pp. 749–750)

The patient's account reveals the frightening experience of an idea of reference, where the simple act of listening to a radio leads to a sense that whatever is being said refers "to me." The account also reveals a loss of self ("I forgot who I was and what I believed in"). The extremity of this loss reminds the student/reader of what it would be like to lose identity—for example, the new identity of a medical student and healer.

A corollary view of the loss of the self is given by the mother of a son with schizophrenia (Ben-Dor, 2001). She describes the slow "death" of the son she once knew.

> My son was already long gone, dying bit by bit over the 16 years of his battle with schizophrenia. . . . I had never had a real chance to say goodbye to David. He had disappeared into his illness so slowly, imperceptibly. (pp. 329, 332)

This is often a new realization for the student/reader: that parents grieve for the people they knew before their children were overcome by the illness. As with Alzheimer's disease, the family members watch and mourn as mental illness ravishes the minds and personalities of their loved ones but, with chronic schizophrenia, the loss occurs at a much younger age and proceeds for a long period of time. It is "mourning without end," as one parent/psychiatrist wrote (Willick, 1994).

The Experience of Social Isolation and the Need for Connection

In her first-person account "Schizophrenia and Socialization," Valerie Fox (2009) gives a painful description of her increasing isolation. After the onset of her "journey with schizophrenia" at age 21, she loses her one close friend, along with family members.

> Today I think about when I left my family, which was my center; with no family around me, there was no distraction to my racing, intense thoughts—no distraction from schizophrenia's taking a firm hold. Once I grew out of the family unit and became independent, my thoughts were my guide to living, and they were ill; my judgment was not sound. I struggled for a few years until I realized that with schizophrenia I could not trust my thoughts alone and needed supports. (p. 430)

She loses her marriage and the relationships with her children before gaining another friend:

> It had been about 35 years since I allowed myself the pleasure of a close friend, and I am enjoying having someone to share both the good and bad experiences in my life and to have someone who is always supportive. (p. 431)

The book *Henry's Demons* (Cockburn & Cockburn, 2011) reveals that, despite the fragmentation of consciousness and sense of self caused by schizophrenia, Henry retains an emotional connection to his family and friends. During his first hospitalization, when he is refusing medication, his mother cries and says: "I can't take this anymore. I can't face the fact, Henry, that you may never get well." At this moment, faced with his mother's emotional distress, Henry replies, "Well, all right, then, I will take the olanzapine" (p. 26). At another point, Henry describes how his best friend "persuaded me to take the pills, as it was the only way I could get any fresh air" (p. 90). These reactions allow the student/reader to see that hospitalized patients with schizophrenia seek human connections, no matter how unemotional and without affect they may appear.

The Therapeutic Relationship

In his family account, "More Magic Bullets?" Jay Neugeboren (2008) describes the treatment of his brother, Robert, who is hospitalized with psychosis, and what happens to Robert when he loses an important relationship.

> Ten years ago, Robert was put on a new antipsychotic medication and responded so well that the staff at his hospital, who had previously thought Robert might have to spend the rest of his life behind locked doors, got him ready for discharge. Then one morning, in a total panic, Robert telephoned. "Alan's leaving!" he shouted. "Alan's leaving!" Alan was Robert's social worker, with whom he had had a good long-term relationship, and Alan had been transferred overnight to another hospital. The result? Robert decompensated completely, and it was another year before he would again be readied for discharge. The question, then: why did the medication that worked so well on Monday stop working on Tuesday? (p. 143)

Years later, for a book he is writing, the author interviews individuals in recovery. He asks them what made the difference: "In all instances, they said that the key had been a relationship—the presence in their lives of somebody—professional, family, or friend—who believed in them, who talked with them, and who was committed to staying with them for the duration" (p. 144).

This view is echoed in a memoir by Elyn Saks (2007), who suffers from severe schizophrenia with paranoia. She is highly intelligent and determined and comparatively lucid between bouts of auditory hallucinations and regressions into cognitive and emotional disorganization. After years of study, she graduates from law school and becomes a law professor. In her memoir, she describes her earlier treatment at a hospital in England:

> I trusted Dr. Hamilton immediately. . . . He effortlessly made jokes; he spoke to me as though we were friends; he seemed to care about me. I looked forward to our appointments, no matter how difficult the conversations were. It was human contact, and I craved that. . . . I adored Dr. Hamilton, and I would have done anything to get better for him. Freud had picked up on this phenomenon in the early 1900s; he labeled it the "transference cure." (p. 70)

In Saks's book, the student/reader finds a model for the power of a successful therapeutic alliance. The student learns that, despite doing everything "according to the book," including the use of empathy, there might not be a connection. If the doctor is not emotionally awake, so to speak, an alliance may never form.

Stigma

The struggle to deal with stigma is ongoing for patients and families. A woman with schizophrenia talks about how difficult it is to make a friend—"it is like trying to land a Mars

lander on Mars"—and how difficult it would be to find a partner because of stigma (Parker, 2001).

> If I ever found a potential life partner, I would eventually have to divulge my mental illness. I would, however, be in a quandary as to when to reveal that I have schizophrenia. A revelation that came too soon could cause the dissolution of the relationship because of fear and stigma. Would I ever be capable of "losing it" and endangering other people, especially people I love? . . . A revelation that came too late could also end the relationship because the partner might feel as if I had been lying throughout the relationship. (pp. 717–718)

A mother struggles for 16 years to find a way to help her schizophrenic son (Ben-Dor, 2001). She also has two young daughters.

> My then 13-year-old daughter summed it up this way: "If David's body were hurting, people would send gifts, but because it is his mind that's hurting, they throw bricks." And so we were thrust into the stigma/blame loop. "She's the one with the crazy son. Maybe he's crazy because she is?" My response? "I'm the one with the healthy daughters. Are they healthy because I am?" (p. 330)

When treating patients with medical illness, the student has little sense of the power of stigma; there is less prejudice toward medical illness than toward mental illness. In our culture, the seriously mentally ill are often feared and excluded (Rüsch et al., 2005); by reading personal accounts, the student/reader can begin to discern if he or she has stigmatizing attitudes toward these patients.

Coping

A number of first-person accounts provide coping strategies for persons with schizophrenia. In "How I Perceive and Manage My Illness" (Leete, 1989), the author writes, "Taking responsibility for my life and developing coping mechanisms has been crucial to my recovery" (p. 197). She summarizes her coping strategies as follows:

> Many of us have learned to monitor symptoms to determine the status of our illness, using our coping mechanisms to prevent psychotic relapse or to seek treatment earlier, thereby reducing the number of acute episodes and hospitalizations. My own personal warning signs of decompensation include fatigue or decreased sleep; difficulty with concentration and memory; increased paranoia, delusions, and hallucinations; tenseness and irritability; agitation; and being more easily overwhelmed by my surroundings. Coping mechanisms may include withdrawing and being alone for a while; obtaining support from a friend; socializing or otherwise distracting myself from stressors; organizing my thoughts through lists; problem-solving around specific issues; or temporarily increasing my medication. (pp. 199–200)

On the psychiatry clerkship, the student is given an overview of coping skills that patients use. However, coping skills, like early warning signs, are individual. Elyn Saks and others (Saks, 2013) have been meeting with individuals like herself, with "high-functioning schizophrenia," to understand how they succeed in their jobs and studies. What they do is identify triggers and develop techniques "to keep schizophrenia at bay." First-person accounts help prepare the student/reader to discuss these specific strategies with patients.

Recovery

Recently, psychiatric approaches to treatment and rehabilitation have included the perspectives of people in recovery, including "the varying views of psychiatrists, psychologists and other highly trained persons who themselves have been diagnosed and treated for schizophrenia" (Frese, Knight, & Saks, 2009). According to a first-person account by Scotti (2009), recovery can lead to new meanings and possibilities. The author was a chemistry student studying for a master's degree when he was hospitalized for schizophrenia, and his recovery was slow. He retrained as a dental technologist but was unable to keep a job. He retrained as a peer-support worker and found employment on a psychiatric Assertive Community Treatment team.

> They say that recovery is knowing oneself under new circumstances, redefining one's role, and reevaluating oneself to develop a new sense of respect of oneself. After living in darkness for many years and having died to my old self, thinking that my life was over and futile, a new birth emerged from within me that has made my life more meaningful and purposeful than before. Whereas before I was a ''thing'' person, I now discovered a part of me that is a ''people'' person. I treasure relationships. . . . All the pain and suffering of the past was not a waste because it has helped me to be more human in that now I feel I am a more compassionate and empathic person, and I can use that new enlightenment to help others. (p. 846)

On the psychiatry clerkship, students fear they will not be able to help patients or effect change in their chronic conditions. Students are taught that expectations are different for patients with serious mental illness, as there is currently no cure. First-person accounts reveal the possibility of recovery and teach the reader that every recovery—and every expectation for recovery—is different.

DISCUSSION

There are limitations to this paper. The narratives have been shortened to meet space requirements, but we have included all references, should instructors want to return to the original narratives. Ideally, on a psychiatry clerkship where most students do not choose psychiatry as a career path, narratives of other disorders, such as anxiety, mood, and psychosomatic disorders (LeCroy & Holschuh, 2012), would be helpful. The narratives reproduced here have been used on a state hospital clerkship, where schizophre-

nia is common, and many of the concepts could translate into work with other patients.

Another difficulty is the lack of evaluation. Possible avenues for evaluation include surveying the students on the effectiveness of individual narratives in teaching the objectives outlined in Table 2, and testing the effect of the early use of narratives on the clinical encounter with patients.

There has been an ongoing discussion in the literature about the value of using mental-illness narratives to train healthcare providers, and a movement has evolved to try to increase our understanding of the factors that shape the narratives. For example, Baldwin (2005) discusses the mental patient's loss of ability "to construct and articulate a coherent narrative" due to language and cognitive difficulties. Donohue-Smith (2011) has developed a conceptual model and checklist for evaluating the "influences" on the mental-illness narrative. This approach is beyond the scope of this paper.

CONCLUSION

While reading narratives written by persons with mental illness, the student can internalize a picture of each person he or she meets in a narrative. These people, in turn, become "touchstones" in the student's mind when encountering patients in the hospital. They become a source from which to extrapolate further meaning or understanding, much as a psychiatrist with twenty years of experience might draw on his or her knowledge from encounters with previous patients. Furthermore, by reading narratives, the student can move from the study of symptoms and differential diagnoses into the experiential realms of identity, relationships, recovery, and hope.

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Conflict of Interest Disclosure

The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. No conflicts were noted.

Author Contributions

The authors had equal roles in writing the paper.

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The Metamorphosis of a Horse into a Zebra: A Case of Primary Eosinophilic Gastroenteritis

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Chronic diarrhea is a common diagnostic entity faced by many primary care physicians. Primary eosinophilic gastroenteritis (PEG), a relatively rare but not uncommon cause of chronic nonbloody diarrhea, presents with nonspecific symptoms, making clinical consideration and diagnosis extremely challenging. In PEG, eosinophils selectively target the gastrointestinal tract, where they degranulate, causing inflammation and irritation. We report the case of a 46-year-old female with recurrent hospitalizations for nausea, vomiting, and diarrhea over a nine-month period. After an extensive workup ruling out secondary causes of eosinophilia, she was diagnosed with PEG.

INTRODUCTION

Chronic diarrhea is a common diagnostic dilemma faced by many internists. First reported by R. Kaijser in 1937, primary eosinophilic gastroenteritis (PEG) is associated with eosinophilic infiltration and degranulation in the digestive tract (DT). Presentation is often nonspecific but commonly depends on the depth of eosinophilic infiltration in the DT. While diagnosis is based on clinical symptoms and a biopsy specimen, peripheral eosinophilia is commonly absent. Herein, we describe a patient with multiple hospital admissions for diarrhea, who was ultimately diagnosed with PEG.

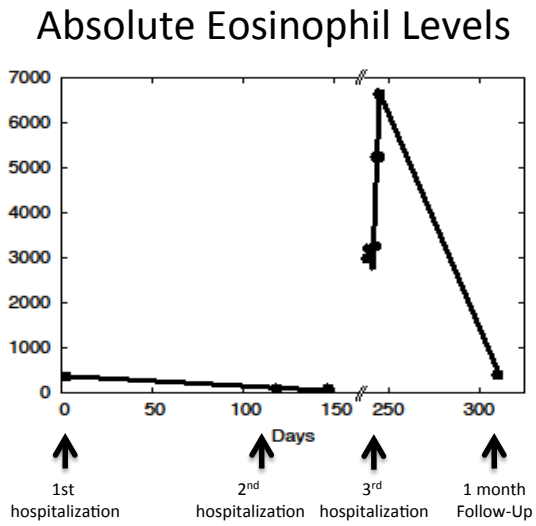
CASE PRESENTATION

We report the case of a 46-year-old female with no past medical history who presented with recurrent hospitalizations for relapsing remitting abdominal pain and diarrhea over nine months. On two prior hospitalizations, no fever or eosinophilia was reported, and she received metronidazole with a working diagnosis of bacterial gastroenteritis (Figure 1A). Five days prior to admission, she had developed cramping epigastric pains and five to 10 episodes of foul-smelling, yellow, nonbloody, watery, mucousy diarrhea. Upon her arrival in the emergency room, her vital signs were within normal limits. A physical exam revealed hyperactive bowel sounds and mild tenderness throughout the abdomen. A rectal examination revealed light-brown guaiac-negative stool. She had an elevated white blood cell count (14,200) with a differential showing elevated eosinophils (25%, 2,820; Figure 1A). IgE levels were elevated (2130/ul; *n* = < 180/ul). An abdominal computed tomography scan was unremarkable. Infectious labs, including *Clostridium difficile* toxin and stool for ova and parasites x3, were negative. Further evaluation revealed a normal ANA panel, thyroid function tests, folate and vitamin B_{12} levels, and fecal fat and electrolytes. A duodenal biopsy specimen demonstrated chronic enteritis with villous shortening, crypt hyperplasia, regeneration, and increased stromal mononuclear (eosinophil) inflammation and infiltration (Figure 1B). She was diagnosed with PEG. While hospitalized, the patient was advised to adhere to an elemental diet. Her symptoms improved within one week without medication and she was followed up closely as an outpatient. At her one-month follow-up, she reported decreased pruritus, drowsiness, and frequency of diarrhea. She was able slowly to advance her diet. Her IgE and eosinophil levels began to trend down (983 and 600/ul respectively; Figure 1A) without therapeutic intervention. Continuous monitoring was initiated in the clinic to screen for a relapse of symptoms.

DISCUSSION

Pathogenesis

Eosinophils are created in the bone marrow and, following exposure to growth factors, mature and relocate throughout the body. They can be found at different levels throughout the gastrointestinal system (e.g., 0/high power field [hpf] in the esophagus and up to 68/hpf in the appendix) and play a protective role, especially in fighting parasitic infections (DeBrosse, Case, Putnam, Collins, & Rothenberg, 2006; Khan & Orenstein, 2008). Eosinophils are activated by the TH2 cellular pathway through proinflammatory stimulant cytokines such as IL-4, IL-5, and TGF-ß (Khan & Orenstein, 2008). Studies have shown an increased production of TH2-associated cytokines (IL-41 and IL-5) in PEG (Jaffe et al., 1994). The precise trigger for increased tissue eosinophilia in PEG remains elusive. Recent evidence points to an interplay between genetic and environmental factors. For example, a positive family history is present in up to 10% of patients with PEG (Guajardo et al., 2002). Alternatively, the observation of a high correlation between PEG and atopy and food allergies may indicate an environmental trigger. This is further supported by multiple observations that PEG can be ameliorated or even reversed with a change to an elimination or elemental diet (Khan & Orenstein, 2008; Méndez-Sánchez, Chávez-Tapia, Vazquez-Elizondo, & Uribe, 2007; Zuo & Rothenberg, 2007).



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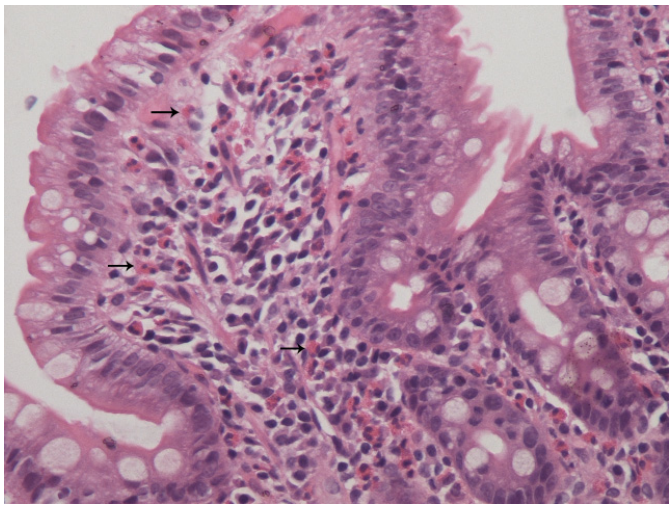

B

Figure 1 | Eosinophil Levels and Intestinal Biopsy. (A) Absolute eosinophil levels on two previous hospitalizations and current admission (third hospitalization), as well as at one month post current admission. (B) Photomicrograph of small intestine biopsy showing increased eosinophils (arrows) and chronic inflammatory cells in the lamina propria with villous architecture preservation and no intraepithelial inflammation (making celiac disease, autoimmune mediated injury, or infections unlikely).

Presentation

PEG has been dubbed a "great imitator" due to its variable and nonspecific symptoms, making clinical consideration and diagnosis extremely challenging. Common symptoms include abdominal pain (most common, in up to 75% of patients), nausea, vomiting, diarrhea, and anorexia (Méndez-Sánchez et al., 2007; Talley, Shorter, Phillips, & Zinsmeister, 1990). Some have reported PEG presenting similar to intussusceptions (Huang, Ko, Huang, & Lee, 2001), pyloric stenosis (Khan & Orenstein, 2000), appendicitis (Tran, Salloum, Tshibaka, & Moser, 2000), pancreatitis (Le Connie & Nguyen, 2004), and ascites (Khalil & Granieri, 2003).

Level of eosinophilic infiltration is strongly associated with presenting symptoms. Mucosal predominant pathology commonly presents with a protein-losing enteropathy, malabsorption, nausea, vomiting, and diarrhea (Mason & Andablo, 2003). Alternatively, muscularis-predominant infiltration presents with intestinal obstruction (Khan and Orenstein, 2008), while serosal-predominant infiltration presents with ascites (Khalil & Granieri, 2003). Mucosal involvement is most common (up to 100%), with serosal involvement least common (up to 40%); however, these findings may be due to the ease of obtaining mucosal tissue on routine endoscopic biopsy as compared to serosal tissue, which necessitates a full thickness biopsy (Khan & Orenstein, 2008; Talley et al., 1990).

Diagnosis

Diagnosis of PEG is based on gastrointestinal symptoms, exclusion of any known causes of eosinophilia in the DT (e.g., neoplasm, drug interactions, parasitic infection), and a positive biopsy sample. Peripheral eosinophilia is commonly absent (>50% of the time [Sleisenger & Fordtran, 1993]), and not necessary in the diagnosis of PEG. Furthermore, degree of peripheral eosinophilia, if present, has not been correlated with severity of eosinophilic infiltration in the intestinal system (Huang et al., 2001). The sensitivity of endoscopic biopsies may be low due to the variety of permeating patterns (patchy vs. continuous) and layers of infiltration (Simon, Wardlaw, & Rothenberg, 2010). Endoscopically, macroscopic signs of mucosal inflammation are uncommon, but may include ulcerations and friability. Microscopically, histopathologic evidence consists of analysis of eosinophil density, degranulation, and absence of other disease features. Diagnosis of muscular or serosal involvement requires an open biopsy via laparotomy or laparoscopy.

Treatment

To date, there are no random controlled trials or definitive treatments for PEG. Diet modification to an allergen-free or gluten-free diet has been reported as helpful in ameliorating or even reversing symptoms as well as reducing the need for medical therapy (Méndez-Sánchez et al., 2007). Glucocorticoids have been the standard medication for management of those who fail diet alteration. Acceptable responses have been reported using prednisone (20–40 mg) for four to eight weeks (Khan & Orenstein, 2008; Vara-Thorbeck, Toscano-Mendez, & Osorio, 1997). Overall, experience has demonstrated varying responses from complete remission to a chronically relapsing pattern (Khan &

Orenstein, 2008; Lee et al., 1993). Therefore, due to the side effects of long-term steroid therapy, many attempts have been made to find more-targeted immunotherapy. For example, small trials have demonstrated successful outcomes using immunomodulators such as Montelukast, Suplatast, and Omalizumab (Foroughi et al., 2007; Quack et al., 2005; Shirai et al., 2001; Stein et al., 2006).

CONCLUSION

PEG is a rare but not uncommon disease that should be considered in the differential diagnosis for chronic relapsing nonenterohemorrhagic diarrhea. This case highlights the need for a heightened degree of clinical suspicion to diagnose PEG due to its varied presentations, and often normal laboratory values without peripheral eosinophilia. While our patient improved without medical therapy, a definitive diagnosis explained her chronic debilitating symptoms. This led to relief for both the patient and the physician, and allowed for close follow-up with a known focus. Increasing physicians' awareness of PEG may help those suffering from its debilitating symptoms.

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Conflict of Interest Disclosure
The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. No conflicts were noted.

Author Contributions
All authors had access to the data and an equal role in writing the article.

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The Rise and Fall of Authoritarianism in the Teaching of Medicine

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The spring of 1903 arrived in Baltimore on schedule, and the trees and flowers on the campus of the Johns College of Medicine were already in bloom. But the medical students scurrying to the amphitheater hardly noticed. Sir William Osler was waiting with a patient, and heaven forbid they should be late.

Sir William was a remarkable figure in the history of American medical education (Geyman, 1983). Born and educated in Canada, he did his graduate work in England, Scotland, Germany, and Australia. Following his arrival at Johns Hopkins, he reorganized the curriculum, combining the English system and the German internship and residency systems. There were two years of clinical clerkships, with small-group teaching at the bedside. Central to his teaching was his textbook: *The Principles and Practice of Medicine* (Osler, 1892). That day, he planned to discuss a section on cardiac dilatation. He had already mastered the lecture; he had written virtually every word of the book.

The students had spent the night memorizing the section, which focused on history and physical manifestations, since little was known at the time about disease mechanisms, laboratory findings, or treatment. Osler may have taken this avoidance of therapy to the extreme; indeed, Hogan (1999) wondered whether Osler had "paranoia antitherapeuticum baltimorensis." Still, Osler remains among the immortals.

Osler eventually turned over the updating of his textbook to Henry Christian, who continued the practice of writing the entire text himself. Christian argued that "there is an advantage in presentation by a single author, who has studied the reports of others in the light of his personal knowledge and experience, and presents the various subjects with a unity of critical thought as is not possible in multiple authorship." Authoritarianism indeed! Edition after edition appeared, with no outside contributors. *Principles and Practice* lost value, and finally ran aground.

Fortunately for American medical education, a new, multiauthored book under the editorship of Russell Cecil, *Textbook of Medicine*, appeared in 1927. Experts in their fields wrote each chapter, and disease mechanisms and therapy were in abundance. With Cecil's work as a model, Harrison's *Principles of Internal Medicine* (Harrison, 1950) was published. Harrison's book and similar texts are now used throughout the world.

STUDENTS AND RESIDENTS

With the advance of the materials of medical education, we might ask about the students themselves. Here, a paradox appears: students at many schools continued to be subject to professorial authority, receiving rigorous and sometimes ruthless questioning and contributing few of their insights during the rituals of teaching. Dr. Sam Ziegler, Einstein Class of 2002, showed me the memoirs of his grandfather, Dr. Samuel R. Ziegler, who entered Case Western Reserve Medical School in 1936, and recalled the following experience (Ziegler & Ziegler, 1999):

> I had another of those real hair-raising experiences to start off my sophomore year. One of the subjects we took was Pathology. Dr. Harold Karsner was the instructor. Dr. Karsner had the reputation of being very hard on students. I was again afraid that I was going to be the first to be called on with my name beginning with a "Z". I prayed he would start with the "As" when we walked into the amphitheater for our first class. But what did he do? He started with the "Zs". He called out "Ziegler!" And asked me a question that had something to do with syphilis and serology.
>
> I finally replied, "Dr. Karsner, I don't know." I then stammered out some half-assed answer after a short pause during which Dr. Karsner continued to look in my direction. Dr. Karsner took another long drag on his cigarette, inhaled deeply and said "Ziegler, I don't see how you can be so goddamn dumb." You could have heard a pin drop in the amphitheater.

This state of affairs went on in our schools—perhaps not so colorfully—for a surprisingly long time. I, like many of my contemporaries, recall professors who were brilliant but seemed to delight in demolishing students. Students were not the only victims; interns and residents were driven to exhaustion by long hours of service and relatively little supervision. Indeed, it could be argued that when reform came, it started with the plight of the members of the house staff.

In 1957, interns and residents in New York City's public hospitals took leave of their roles as underpaid and overworked apprentices in what has been termed one of the "last great sweatshops in America" (Duncan, 1996), and founded the Committee of Interns and Residents (CIR). In 1969 they were joined by house staffers in the private sector. In 1999 the CIR won a National Labor Relations Board decision guaranteeing residents in private teaching hospitals the right to form unions. The CIR went on to negotiate contractual limits for on-call schedules, benefit plans, and higher pay.

Figure 1 | The learning studio at the University of Virginia School of Medicine. This is a building designed to accommodate students gathered around conference tables, and conferring with each other on the answers to questions projected on the screens above. Permission to reprint granted by Norman Shafer (*University of Virginia Magazine,* spring 2011, pp. 36–37).

The movement gained strength following a tragic event in 1984, in which Libby Zion, an 18-year-old girl with a complex history of drug use, was admitted to a New York hospital with fever and agitation. The admitting intern was beset with other patient problems, and Libby died of cardiac arrest. Her father, Sidney Zion, a journalist, took up her cause and "set in motion a series of reforms, notably work hour limitations instituted by the ACGME that have revolutionized modern medical education" (Lerner, 2006). Dr. Bertrand Bell of Albert Einstein College of Medicine headed a panel of experts that recommended that residents could not work more than 80 hours a week or more than 24 consecutive hours.

THE MEDICAL CURRICULUM

There has been a profound and heartening change in the approach to teaching medical students, brought about by a deeper understanding of the teaching process and a greater respect for the ability of the students to teach themselves and each other. After all, they are college graduates, and have already gone through a meaningful process of achievement and reflection. One need only survey the home pages of our medical schools to appreciate the variety and imagination that have gone into their curricular design. A list of some of the newer programs would include the following:

1. Earlier encounters during the preclinical years with patients, who share their stories with students.
2. Problem-based learning, in which students work in small groups to deal with scenarios designed to simulate real-life cases.
3. Evidence-based medicine, in which students learn to evaluate new drugs and new findings in the search for effective therapies.
4. Students-as-teachers programs, in which third- and fourth-year students take on the role of teachers for small groups of first- and second-year students. This program has been in use at Einstein, and has been favorably reviewed by both teachers and students.
5. The opportunity for students in their clinical training periods to return to basic science in the form of classroom teaching during their work on the wards. Also, at Einstein, under the guidance of Dr. Jeffrey Avner, students taking pediatrics are asked to include a "basic science paragraph" in their admission writeups. This serves not only as a reminder of their preclinical studies, but as a means of giving their preceptors and attending physicians an update on the latest in the basic science of the disease at hand: the student as professor, if you will.
6. The opportunity for students to take an extra year or two to obtain advanced degrees in areas such as public health and business administration.

7. Team training, moving the student "toward being an effective and competent team player and not an individual achiever" (Morrison, Goldfarb, & Lanken, 2010), in preparation for the growing need for cooperative approaches to healthcare management (Figure 1).
8. Finally, the Internet. Many of our current students may have come from colleges where the Internet has played a major role in their education. At least two articles in the *New York Times* have surveyed the role of the Internet in today's college education (Parry, 2012; Lewin, 2012). At the extreme, the Internet has supplied much of the information that students receive, has influenced their choice of courses, and has even identified appropriate partners for them in the learning process. Inevitably, the Internet is now having an impact on medical education. For example, the syllabus, a printed document so carefully assembled each year as the central source of information for each course, is on the Internet in many schools, and is only part of a flood of sources of information. And, as already noted, it plays an important role in the clinical years.

Some of the programs listed above should, in theory, increase the collegiality among students and the attending physicians and house staffers responsible for their education. But it appears that this is not entirely the case. A recent nationwide poll conducted by the Association of American Medical Colleges (2012) showed that a substantial percentage of students still encountered what they regarded as mistreatment, including public humiliation and gender-based discrimination. More work must be done in this area, which may extend beyond the limits of medical education.

CONCLUSION

This brief commentary has taken us from the early days of medical education, when a few authorities dominated the source of medical knowledge, to the computer age, when students and teachers share the information provided by the Internet. But rest assured: teachers still have much to contribute in terms of experience, perspective, and examples of kindness toward patients seeking their help. Sir William Osler would be grateful to know this.

Conflict of Interest Disclosure

The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. No conflicts were noted.

Acknowledgments

This article builds on an article written for *MedEd@AECOM,* "Students as Teachers: An Idea Whose Time Has Come" (Hays, 2004). The author would like to thank Dr. Albert Kuperman for his leadership and encouragement during the years he served as associate dean for educational affairs. His enthusiasm and wise counsel meant everything to me in my work at Einstein. Colleagues who have contributed their thoughts to this article are Dr. Gerald Appel, Dr. Jeffrey Avner, Dr. Bertrand Bell, Dr. Michael Risley, and, finally, my wife Susan, who patiently corrected my liberties with the English language.

Editorial Note

Dr. Richard M. Hays passed away on November 22, 2012.

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Process and Experience of Creating a Student-Run Step 1 Guidance Program

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We developed the Albert Einstein College of Medicine USMLE (United States Medical Licensing Examination) Step 1 Guidance Program in the fall of 2010. The objectives of the program were twofold: to provide reliable, unbiased advice on Step 1 preparation, and to reduce student anxiety surrounding the examination. The program aimed to fill a void for the students by focusing on the process of preparing for the test. It was not intended to teach Step 1 content, but instead to help students study effectively and efficiently. In our opinion, the most significant service medical students required was assistance in developing a personalized program of study for this examination.

This program was conceived, implemented, and continually reviewed by students. It is our hope that this bottom-up approach, created by and for medical students, can be easily adapted by other medical institutions and implemented in medical education beyond Step 1 preparation. Faculty and administrators provided necessary resources, and their help was crucial to the success and longevity of the program. This commentary outlines the process and experience of creating this program, which is now in its second year and well established within the Einstein community.

DEVELOPMENT

After completing the USMLE Step 1, we concluded that the most important and daunting aspect of the process was determining how to prepare for this examination. With no shortage of Step 1 study materials and commercial courses (Tompkins, 2011) available, each touting itself as the best and most comprehensive, we were often at a loss when deciding which resources to use. We wanted our guidance program to enable the free flow of reliable information from senior to junior medical students as they began to prepare for the examination. Previously at Einstein, two mandatory classwide meetings, one of which included a student panel, had been held to discuss Step 1. While we had found these meetings helpful, we felt that two meetings alone were not sufficient.

Additionally, the flow of Step 1 information was not ideal. Generally, a small handful of third-year medical students (MS3s) disseminated information to a few second-year students (MS2s), and then this knowledge spread laterally among the remaining MS2s. This structure was flawed in two critical ways. First, the information was "one size fits all" and could not be adapted to specific student concerns. And second, the information was coming from an extremely small group of students, which meant it might not adequately reflect varied points of view. These inadequacies in the student-to-student distribution of information were the primary motivation for the creation of the Step 1 Guidance Program.

Another goal of the program was to reduce student anxiety. As the sole standardized indicator of medical knowledge, often used as a screening tool by residency programs, the results of the USMLE Step 1 are considered one of the most important aspects of a residency application. Of those polled in the 2010 National Resident Matching Program Director Survey, 73% cited the applicant's Step 1 examination score as a factor in interview selection. This represents the largest percentage of all interview selection criteria (National Resident Matching Program, 2010). Medical students, therefore, have a great deal of anxiety about this exam, and such anxiety has been shown to affect performance negatively (Ramirez & Beilock, 2011; Beilock, 2008). Our Step 1 Guidance Program strove to reduce stress not only by providing useful information regarding study resources and methods, but by serving as an outlet for concerns and by providing support when needed. Since peers are often more approachable than supervisors, we believe that a student-run organization is the ideal format to address effectively the pressures and stresses induced by the Step 1 exam.

In order to ascertain the knowledge and experience of a significant sample size, we distributed a survey to Einstein students who had taken the USMLE Step 1 in 2010. Seventy students completed the survey, which focused on student opinions of various study methods and study resources. Its purpose was to assess students' perspectives on the best study resources. We then interviewed 10 Einstein test takers in person to gain more insight. Equipped with this information, we sought to develop a guidance program for those students preparing for the Step 1 examination in 2011.

We developed a four-pronged approach: an online blog with survey results and relevant articles; large-group presentations to advertise our services; personalized email support; and individual meetings. The online blog (http://blog.myalbert.einstein.yu.edu/step1s2s/) is a website created to introduce the guidance program and provide a range of basic tutorials on how to study for the examination. Articles include a student guide to the basics of Step 1, instructions for creating a study schedule for Step 1, and study resources based on the 2010 student survey results.

In the beginning of the academic year, we conducted an hour-long presentation for the MS2 students in order to introduce our program, its purpose, and the services it provided. Email correspondence was available for specific questions from students who preferred to remain anonymous among their peers. Individual meetings were aimed primarily at helping students create a personalized study schedule. To facilitate easy access to the group, we held open office hours near the area where most students studied. This allowed them to see us quickly and easily when questions arose. We found, however, that students often came to these sessions for reassurance rather than to have specific questions answered.

Faculty support was sought early on in the development of this program. We presented the concept of the Step 1 Guidance Program to the deans of students, who both fully supported our project. Gaining the support of the school administration added authority to our program. Moreover, we worked closely with the staffers at the office of academic support and counseling, who referred many struggling or nervous students to our program. The success and stability of the Step 1 Guidance Program are largely attributable to the assistance and guidance we received from the Einstein administration and faculty.

REFLECTIONS

We believe that our four different services effectively and efficiently provided information about the Step 1 exam, as well as appropriate study methodologies. Most students started with the large-access media—the blog and group session—and then followed up on more-specific concerns via email or during our office hours to obtain customized help. This allowed for the maximal distribution of advice and information.

In "Money for Nothing?" Tompkins (2011) correctly identifies a frightening trend in Step 1 preparation: the rise of for-profit preparatory services. To date there have been several studies revealing no benefit from these commercial courses, including Kaplan live courses, Falcon review courses, and Doctors in Training (DIT) (Werner & Bull, 2003; Scott et al., 1980; Lewis & Kuske, 1978). Despite the findings presented in this literature, commercial courses are thriving. Some of this may be explained by the marketing approach implemented by these for-profit companies. One particular company visited the Einstein campus and gave a lecture advertising its "foolproof" Step 1 preparation system in early October. The timing of this visit was crucial, as it was prior to most students having obtained adequate knowledge of all the available resources. While Einstein does not endorse or invite specific vendors to the campus, the commercial company granted one student a free course in return for organizing and setting up a meeting. As a result, a corollary goal of the program was to inform students of the advantages and disadvantages of commercial company services, prior to the arrival of those services on campus.

CONCLUSION

To hone the program for future students, we sent a detailed survey to the 2011 exam takers with the goal of objectively determining which methods of preparation correlated with higher Step 1 scores. The data gathered from this research project will influence future Step 1 preparation advice and improve the guidance program. Two new students were selected to continue the program for the coming year. It is our hope that this program will continue to evolve and be of great use to future Einstein students.

Our experience has shown that medical school curricula can be significantly augmented regarding USMLE Step 1 preparation through student-led initiatives. The "near-peer approach" of this guidance program was beneficial to us and to the many students involved. Unforeseen benefits, such as protecting our students from being taken advantage of by the commercial USMLE preparation industry, have also arisen from our project. We strongly encourage medical students at other institutions to create similar programs for the benefit of their peers.

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Conflict of Interest Disclosure
The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. No conflicts were noted.

Author Contributions
The authors had equal roles in the writing of the manuscript.

Editorial Note
Dr. Sharon Silbiger passed away on September 6, 2012.

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A Perspective on the Relationship between Jacobi Medical Center and Albert Einstein College of Medicine: In the Days of the Giants

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The story of Jacobi Medical Center and its affiliated medical school begins decades before their opening in 1955. During the Great Depression and the Second World War, little hospital construction was completed in New York City. By 1948, a postwar population boom had created a crisis of hospital overcrowding. This was compounded by an uncontrolled tuberculosis (TB) epidemic. Streptomycin had been discovered in the 1940s, but no effective combined drug/chemotherapy treatment for TB existed; victims lingered in sanitariums or hospital TB wards, and the public was increasingly afraid to enter municipal hospitals for fear of contagion.

Then Mayor O'Dwyer authorized five new hospitals, the largest two to be built first in the underserved borough of the Bronx. Despite considerable controversy, this effort was financed by an unprecedented nickel rise in the cost of a subway token. A vacant 64-acre site on Pelham Parkway was chosen, where the largest racetrack in the United States, the Morris Park Racecourse, had operated until 1904. Before its decline, this was the largest and finest racetrack in the country, with stalls for more than 1,000 horses. The first hospital to be built was a 500-bed TB hospital; it was named after a prominent Bronx doctor, Nathan Van Etten. The hospital was constructed with open-air decks to maximize TB patients' exposure to sun and fresh air. Van Etten Hospital was located at the southernmost tip of the property to keep it as far away as possible from the larger, general medical hospital at the northern end. That facility was named for Abraham Jacobi, who has been called the father of American pediatrics. Jacobi had been a revolutionary in Germany, a friend of Karl Marx, and came to this country as a political refugee. He became the first academic professor of pediatrics in the United States, founded the first section of pediatrics in the American Medical Association, and later served as that organization's president. Although he died years before Jacobi Medical Center opened, his daughter attended the dedication ceremonies and expressed deep pleasure that he had been remembered in this way.

The two-hospital site, known as the Bronx Municipal Hospital Center (BMHC), offered a number of advantages. By the early 1950s, the country was in the midst of the Cold War, and the city fathers were fearful of an atomic-bomb attack. These new hospitals were on the periphery of the city and would be expected to survive an atomic blast centered on Manhattan. They were near rail, water, and highway evacuation routes. Jacobi was built with enormous basements and sub-basements that were reinforced with thick concrete walls and designed to serve as mass fallout shelters. Fortunately, they were never used for that purpose.

At the same time, a small Jewish university, Yeshiva, petitioned the New York State Board of Regents for permission to open the first new medical school in the state in 50 years. Prompted by rampant anti-Semitism in the established medical schools, especially in the Ivy League, Yeshiva's new school would offer a refuge from anti-Jewish quotas and barriers to career advancement.

By today's standards, that discrimination was appalling. One of the founding professors came to Einstein from Yale, where he had sat on the medical school admissions committee. The Yale admissions committee in those years was given two stacks of applications. Each application in one pile was marked with an "H" in the upper left corner. The "H" stood for "Hebrew." The admissions officers were permitted to accept only a few from that pile, no matter how tall it got. The bulk of the acceptances were drawn from the other pile of applications, the ones without an "H."Dr. Bertrand Bell recalls that when he showed up for his interview at Columbia, the dean demanded to know where he had gotten his name. When Bell said his father had changed the family name from Bilotsky, that ended the interview.

When the new school's founders, led by President Samuel Belkin, first approached Albert Einstein, the most famous scientist in the world, for permission to use his name, he was reluctant. But in 1951 Einstein replied in a letter that he strongly supported the new school because Yeshiva promised full equality for all people, regardless of "creed or race." That document, far ahead of its time, remains on display on the campus of Albert Einstein College of Medicine. In 1954, Yeshiva and New York City signed an affiliation agreement between Jacobi Medical Center and the new Albert Einstein College of Medicine. From the beginning the institutions shared a mission. All but one of the founding academic chairs at Einstein were based at Jacobi, and it was the primary teaching and research site for the school. Progress came slowly, but it eventually arrived. The first class at the medical school in 1955 included three women out of 53 students; the next year five women joined a class of 90, which included one African American. Many more women and people of color would enter in the coming years as a greater number of qualified applicants appeared, liberated

by the changing times. To its credit, Einstein established the first program to recruit and retain African American medical students.

By 1955, the anti-Communist hysteria of Joseph McCarthy was in full swing. Many faculty members came to Einstein and Jacobi because of their progressive politics. One example was the pioneering cell biologist Alex Novikoff, best known for characterizing the Golgi body and the lysosome. Novikoff had been fired by Brooklyn College and the Vermont School of Medicine because he had been a member of the Communist Party in the 1930s. He found a refuge and was permitted to continue a productive career in the Bronx. These progressive-minded scientists and doctors influenced the culture at Einstein, which came to focus on primary care, ambulatory care, and preventive medicine.

Eleanor Roosevelt adopted the Jacobi department of pediatrics and was a frequent visitor to the pediatric TB ward. When she visited, she refused to wear a mask, insisting it would frighten the children. (At the time of her death in 1962 from miliary tuberculosis, there was unconfirmed speculation that she had contracted her disease at Jacobi.)

The founding faculty was illustrious. The neurosurgeon Leo Davidoff, a protégé of Harvey Williams Cushing, was the first chair of surgery. Alfred Gilman became the first chair of pharmacology. Irving London founded the department of medicine, and mentored Helen M. Ranney, who pioneered the treatment of sickle-cell disease and went on to become the first female chair of medicine in a university department, at the University of California at San Diego. Henry Barnett, Louis Fraad, Stanley Levenson, Milford Fulop, and many others made seminal advances in their fields. Discoveries in the treatment of congenital heart disease, neonatal jaundice, Tay-Sachs disease, pediatric renal tubular acidosis, Wilson's disease, acid-base disorders, artificial skin, CO_2 laser therapy, and hyperalimentation for burn patients all originated in the Bronx. The diminutive anesthesiologist Gertie Marx developed the spinal needle named after her that is still the standard used for obstetric anesthesia.

The first successful coronary artery bypass in the United States was performed at Jacobi Medical Center in 1961. The 38-year-old patient received a thoracic-artery-to-right-coronary-artery bypass, and survived for a year.

By the time the Van Etten Hospital opened in 1954, isoniazid and ethambutol, antibiotics effective against tuberculosis when used together, had been discovered. This multidrug strategy rapidly made TB victims noncontagious. Tuberculosis had become a curable disease, and when the hospital opened, less than half of Van Etten's inpatient beds were needed for TB patients. M. Henry Williams soon created the first TB home-care program at Van Etten Hospital. By 1970, the TB ward needed only 70 beds, and Van Etten had been converted into a hospital specializing in the treatment of other pulmonary diseases.

The modern era has produced its own challenges, and Jacobi and Einstein have met them. When the AIDS epidemic struck, many fearful New York City doctors shunned infected patients. Jacobi and Einstein rose to the occasion, and doctors such as Carol Harris provided compassionate care during the terrible early years of the epidemic. Jacobi opened the first pediatric AIDS daycare center in the country.

Under Bertrand Bell's leadership, Jacobi conducted early federally funded clinical research studying the care of critically injured trauma patients. This led to the establishment of New York City's first paramedic training program, its first residency program in emergency medicine, and its first pediatric emergency medicine fellowship program. Bell later led the famous Bell Commission, which reformed the education of medical residents in the United States. Meanwhile, Warren Wetzel developed the Jacobi Trauma Service called the JIT, the "Jacobi Institute of Trauma," which served as a model for urban trauma care.

With the passing of time, the relationship between these two great institutions has changed. Weiler Hospital proved to be too small to serve as the university hospital for the medical school, and Montefiore eventually assumed that role. Sadly, in 1995 Yeshiva ended the affiliation contract with Jacobi, weakening a 40-year relationship.

Nonetheless, Jacobi and Einstein still stand side by side. Predictions made in 1995 that Jacobi would cease to exist proved wrong. Jacobi remains a vibrant center for patient care and clinical research. It excels in such areas as emergency and trauma care, and in HIV prevention and treatment. Led by Paul Gennis, the Jacobi faculty developed an independent doctors' group, NYMA, which pioneered a successful physician role in hospital administration. Recently Jacobi provided five acres, including the Van Etten Building, under a long-term lease arrangement that permitted the building of the new Michael F. Price Center for Translational Medicine/Harold and Muriel Block Research Pavilion. Jacobi has a new, state-of-the-art facility.

Jacobi offers the college unique opportunities for medical education. I believe that Jacobi's and Einstein's joint history argues strongly for continued close collaboration. Together, Einstein and Jacobi should plan for the healthcare challenges the future will bring.

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Conflict of Interest Disclosure
The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. No conflicts were noted.

Acknowledgments
Much of the historical material used in writing this brief commentary is drawn from an unpublished manuscript written in 1974 by a Jacobi administrator named Paul Aronson. I also interviewed Drs. Melvin Zelefsky, Ruth Freeman, and Bertrand Bell, who were witnesses to the birth of both institutions.

Prevailing Theories in Cardiovascular Physiology during Ancient and Classical Times

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Currently accepted theories of human physiology have been proposed only in the last two centuries, with understanding of many molecular processes proposed within the last 50 years. However, theories of human physiology have been debated for thousands of years. This paper focuses on the theories of physiology discussed in ancient and classical times, with a focus on the structure and function of the heart and its vessels. The experiments and subsequent conclusions of physicians and philosophers of antiquity have led to some interesting interpretations. Notably, anatomical studies remain remarkably similar to today's understanding, whereas ideas of function and physiology are drastically different.

INTRODUCTION

Human physiology is the study of function in living human organ systems. In the past century, knowledge in this field has been enriched by studies in a plethora of other disciplines, including cell biology, chemistry, physics, genetics, epigenetics, population studies, and even sociological studies. Incredibly, this fund of knowledge is only a recent achievement in the history of human thought. This paper explores the prevailing theories of human physiology during antiquity more than 2,000 years ago, much of it only sparingly in agreement with modern theories. Because the topic of human physiology is vast, the paper will limit its focus primarily to cardiovascular theories in ancient and classical times.

ANCIENT EGYPT

Our knowledge of ancient Egyptian medicine is limited to the preservation of a handful of papyrus scrolls more than 3,000 years old. Through these scrolls we learn that magic and science were part of a single, inseparable concept called *heka* (Veiga, 2009). Like today's physicians, the magician-physicians of ancient Egypt prescribed mixtures of plant and animal products that could have had active ingredients also found in today's medicines (Lefebvre, 1963). In most cases, however, these magician-physicians would invoke spells, recite incantations, or perform exorcisms to cure illnesses; any pharmaceutical prescription was simply an adjunct to the larger healing ritual. Although such practices are illogical and incomprehensible to modern sensibilities, Veiga (2009) suggests that for a predominantly illiterate ancient Egyptian population, the ability to decipher hieroglyphics to perform rituals could seem especially magical and therefore therapeutic. In that case, medical practice in ancient Egypt might have been benefiting from a strong placebo effect.

Despite their penchant for the occult, ancient Egyptian magician-physicians were also familiar with many modern medical topics. Their remedies for conditions such as dislocations and compound fractures remain remarkably similar to treatment today: sutures, brick supports for stabilizing head and neck injuries, wooden splints, and a recipe for creating adhesive plaster (Lefebvre, 1963). Internal diseases familiar to any modern healthcare provider are also described: headache, constipation, dysentery, amenorrhea, cystitis, and even a hematuria that was most likely due to schistosomiasis in the Nile River (Bryan, Smith, & Joachim, 1974). Egyptian medicine was apparently so complex that the magician-physicians were known to be specialists managing single types of disease: there were dentists, ophthalmologists, and even proctologists (literally translated as "herdsmen of the anus") (Nuun, 2002). But above all, these and all other internal diseases were believed to be supernatural afflictions. It therefore followed that an illness of supernatural origin should have a supernatural remedy.

Not surprisingly, ancient Egyptians' understanding of cardiovascular physiology differs drastically from currently accepted principles of physiology. Anatomically, 46 vessels were said to originate from the heart and extend to all the limbs. Through these vessels, the heart controlled all physiological processes of the body (Lefebvre, 1963). For example, certain vessels from the nostrils would carry air directly to the heart; the air would then pass from the heart to the lungs before dispersing throughout the body (Lefebvre, 1963). Other vessels were specialized to carry other bodily fluids such as sperm, urine, fecal material, tears, mucus, and blood. Diseases arose when the bodily fluids existed in abnormally disproportionate amounts in the heart.

Because the heart was also said to be the body's central organ for emotions and consciousness (Lefebvre, 1963; Veiga, 2009), feelings such as sadness and anger were similarly the result of the heart closing itself off from its vessels (Bryan et al., 1974). Despite hieroglyphic language suggesting that the Egyptians attributed arterial pulses to the heartbeat, they seemed to regard the heart as a simple well instead of as a pump (Bryan et al., 1974; Lefebvre, 1963). This anatomical and physiological disconnect might have been due to the mummification tradition, in which the heart was not removed from the body; in the afterlife the heart could then be judged and weighed against the feather of Maat for possible sins against the gods (Veiga, 2009). The ancient Egyptians would therefore have had little opportu-

nity to study cardiac anatomy and infer the heart's possible physiological function.

ANCIENT GREECE

Pre-Hippocratic ancient Greek medicine did not significantly differ from that of neighboring civilizations, including ancient Egypt and Mesopotamia, with respect to superstition and supernatural influence (Longrigg, 1993). Diseases in ancient Greece were thought to be manifestations of a god's anger, and could be cured only by appeasing that god with prayers and sacrifices. The Homeric tales are replete with references to epidemics attributed to the wrath of the gods, and even battle-inflicted wounds represented a spiteful god withdrawing his divine protection in displeasure (Longrigg, 1993). The Greek pantheon also included Asclepius, the god of healing and medicine, whose ritual purifications could cure afflicted believers. The cultural impact of Asclepius remains evident today: his name is invoked in the oft-recited Hippocratic oath, and his serpent-entwined staff, the rod of Asclepius, is still the symbol of medicine and healthcare.

Hippocrates of Cos (ca. 460–377 BCE) was the first physician-philosopher to produce a body of medical theories and observations almost entirely devoid of supernatural, superstitious, and religious references. Today, he is regarded as the father of Western medicine, but he was also heir to a long and vibrant tradition of philosophical thought. The roots of his thinking date back to the sixth century BCE, when a group of thinkers now known as the Ionian philosophers attempted to explain their natural world—from lightning to earthquakes to air—without the trappings of the supernatural (Longrigg, 1993). Hippocrates himself believed that supernatural explanations of disease came from a lack of understanding of natural processes:

> I am about to discuss the disease called "sacred" [epilepsy]. It is not, in my opinion, any more divine or more sacred than other diseases, but has a natural cause, and its supposed divine origin is due to men's inexperience, and to their wonder at its peculiar character. Now while men continue to believe in its divine origin because they are at a loss to understand it, they really disprove its divinity by the facile method of healing which they adopt, consisting as it does of purifications and incantations. (Hippocrates, 1998)

Hippocrates implied that understanding the nature and origin of disease was not just a matter of philosophical or religious debate. Supernatural etiologies were not merely erroneous, but also prevented effective treatment of diseases such as epilepsy.

Hippocrates, like some of his contemporaries—philosophers such as Democritus of Abdera and Anaxagoras of Clazomenae—believed that the human body was a balanced microcosm of the universe that consisted of fire, water, air, and earth. These four elements were endowed with four opposing qualities: the hot, the cold, the dry, and the moist (a principle first espoused by an elder philosopher named Alcmaeon of Croton) (Rothschuh, 1973). Good health required a balanced blend of these elements and qualities. Over time, the Hippocratic physicians developed these principles into the concept of the four bodily humors: the warm and moist blood, the moist and cold phlegm, the cold and dry black bile, and the dry and warm yellow bile (Rothschuh, 1973). (Notably, the concept of different bodily fluids can be traced back to the ancient Egyptians.) Maintaining a healthy mixture of humors required an internal fire located in the left ventricle of the heart, with combustion possible only by breathing air (*pneuma*) and receiving nourishment (Rothschuh, 1973).

Over time, the followers of Hippocrates recognized that the heart contained two ventricles and two atria. A Hippocratic writer even recognized that the atria contracted separately from the ventricles: "one might observe the heart tossing about as a whole, but the ears independently inflating and collapsing" (Katz & Katz, 1962). "Ears" refers what we now call the atria. Hippocratic use of the word "ears" to name the atria persisted to the mid-20th century. Medical texts published in the 1950s termed the left and right atria the left and right auricles, which is an Anglicization of the Latin word for ear: *auricula*. Today, the right and left auricles refer to the right and left atrial appendages. The cardiac valves are similarly described with anatomic precision:

> There is a pair of [veins] at the entrance to which there have been constructed three membranes for each, rounded at the extremity at least, to the extent of a half-circle, and when they come together it is marvelous that they close the outlets, and the end of the veins. . . . If someone . . . removes the heart of a dead man and takes up one of these membranes and bends another up against it, water will not go through into the heart, nor even the breath when forced in. (Katz & Katz, 1962)

The anatomy and function of the cardiac valves were correctly deduced, but no apparent connection was made to their role in ensuring the unidirectional circulation of blood. The Hippocratic writers did not appear to recognize the phenomenon of blood circulation, nor did they believe that the left ventricle was filled with blood. Instead, the bloodless left ventricle was the location of the body's innate internal fire, and the heartbeat was a function of this internal fire. Blood flow was simply the internal motion of a body humor that moved in healthy balance with the other body humors. The movement of blood was postulated to be part of a vague process of all organ development involving blood coagulation (Rothschuh, 1973).

A century later, Aristotle (384–322 BCE) revived the ancient Egyptian belief that the heart and blood vessels were part of a connected system of which the heart was the epicenter. Like the ancient Egyptians, Aristotle believed that the heart was the central organ of the body and the seat of the soul. (Hippocrates believed that the brain was the central

organ of the body.) The heart was the location of the vital internal fire, the site of the body's blood production, and the origin of the body's vascular system. These processes interacted to produce the body's pulse, cardiac contraction, and respiratory movements (Rothschuh, 1973). Newly produced blood in the left ventricle created an expanding heat that caused the chest wall to expand. Inspired air traveled from the lungs to the left ventricle via the pulmonary veins to cool down the blood, resulting in the expiratory movement of the chest (Rothschuh, 1973). When the innate heat expanded again, a pulse-wave pushed blood through all the blood vessels. The blood eventually was converted to organs and tissues, and other fluids of the body were all somehow derived from blood (Rothschuh, 1973). Aristotle's physiology therefore marked an important shift away from the theory of balanced body humors to a physiology based on directionally flowing blood.

Aristotle definitively localized blood to the blood vessels within the body, but some of his intellectual successors wondered if these biological vessels could possibly contain substances other than blood. These hypotheses may have come from Aristotle. He apparently killed animals with chloroform (Huxley, 1879), which left a conspicuous anatomical artifact: dissections prepared in this manner engorged the right atrium with so much blood that it appeared to be continuous with the vena cava (Huxley, 1879). (Aristotle therefore recognized only three heart chambers: the right ventricle, the left atrium, and the left ventricle.) In contrast to the right side of the heart, the left side of the heart and the arteries could have appeared relatively empty (Fulton & Wilson, 1966). If the thickened muscular walls of the arteries did not collapse when empty, in dissection they could appear to be hollow tubes inside the body. This observation left the possibility that the arteries carried only air. The Latin word *arteria* originally referred to the trachea and associated bronchioles.

Herophilus of Chalcedon (ca. 335–280 BCE) was one of the physicians of antiquity who believed that the arteries carried only air. He remains the first and only physician in antiquity to study human cadavers, and he dissected at least 600 of them in his career (Rothschuh, 1973). In these dissections he distinguished arteries as those vessels that were six times as thick as the vessels he called veins (Fulton & Wilson, 1966). Using this thickness criterion, Herophilus concluded that the arterial system was located primarily on the left side of the body, and the venous system was located primarily on the right. Most interesting to him were the pulmonary artery and the pulmonary vein. The pulmonary vein connected to the left side of the heart (an "artery" in Herophilus's system), but it was as thin as a vein. Herophilus therefore called it a "vein-like artery," *arteria venalis* (Fulton & Wilson, 1966). Similarly, the connection of the thick-walled pulmonary artery to the right side of the heart prompted Herophilus to call it an "artery-like vein," *vena arterialis* (Fulton & Wilson, 1966). Both terms would persist through the 17th century CE. Herophilus additionally noticed that the arteries, but not the veins, exhibited a pulsing nature (Fulton & Wilson, 1966), and that the rate of this pulsing was directly related to the respiration rate (Beaujeu, 1963). He therefore concluded that the arteries must contain only air. This conclusion, however erroneous, represented an attention to physiological and anatomical detail not previously witnessed in antiquity.

Erasistratus of Julis (ca. 310–250 BCE), a younger contemporary of Herophilus, agreed that the veins contained only blood, and the arteries held only air. Unlike Aristotle, he believed that blood was created from digested food in the liver, and then moved to the right ventricle by means of the vena cava (Rothschuh, 1973). Inspired air resided in the lungs and moved into the left ventricle by means of the pulmonary vein (the "vein-like artery"). The heart contracted and expelled both air and blood to the entire body via their respective arterial and venous systems, and the heart valves worked to prevent reflux back into the heart (Beaujeu, 1963)—a hypothesis from antiquity that bears some resemblance to the current cardiovascular understanding of unidirectional circulation. Thus, Erasistratus's ideas largely reflect a synthesis of Aristotle's and Herophilus's theories.

Pneuma, not blood, was the primary substance in Erasistratus's physiology. The lungs apparently consumed all blood that entered the pulmonary artery (the "artery-like vein"), and somehow transformed air into a substance called *pneuma* by the time it reached the left ventricle. The *pneuma* was then pumped through the bloodless arterial system, where it could transform again into *pneuma psychikon* in the brain to enable nerves to feel sensation and muscles to contract (Beaujeu, 1963; Rothschuh, 1973). The *pneuma* could alternatively transform into *pneuma zotikon*, which controlled the body's vegetative functions, including moving blood for nourishment of the organs and tissues (Beaujeu, 1963; Rothschuh, 1973).

Like that of Aristotle before him, Erasistratus's physiology advocated active movement of some bodily substance—first as blood in the venous system and then as *pneuma* in the arterial system—but more firmly reconciled his ideas to objective observations.

One argument against the *pneuma* hypothesis was the observation that blood spurted from a cut artery until the animal died, suggesting that arteries did carry blood. Erasistratus therefore postulated that there should be a connection, too small to be seen with the naked eye, between veins and arteries. He called these connections *synanastomoses* (Fulton & Wilson, 1966). Under normal conditions, blood naturally remained in the veins. However, when an artery was cut in a live animal, all the *pneuma* in the artery instantly escaped through the opening and created a vacuum. Because nature abhors a vacuum (a concept called *horror vacui* and advanced by the philosopher Strato of Lampsacos) (Rothschuh, 1973), blood subsequently rushed from the veins through the *synanastomoses* into the arteries and out of the body (Fulton & Wilson, 1966). Without

the technology to refute this hypothesis, the teachings of Erasistratus stood unchallenged for more than 450 years.

ANCIENT ROME

The next great advance in physiology occurred during Roman times under the physician and philosopher Galen of Pergamon (ca. 130–201 CE). Galen was a learned man who was a product of his times. He advocated the Hippocratic theory of humors, and he supported the long-standing idea of the *pneuma* (Rothschuh, 1973). He even agreed with the basic premise of a right-sided venous system and a left-sided arterial system, in which the liver created blood that would ultimately mix with air to form *pneuma*. However, he also conducted numerous animal dissections and experiments that revolutionized the Romans' understanding of human physiology.

Galen's most celebrated achievement in cardiovascular physiology, in direct opposition to the ideas of Erasistratus, demonstrated that blood actually resided within the arteries. He isolated a single dog's artery from all other tissues and tied that artery in two places. By cutting into the artery between the two tied knots, Galen demonstrated that blood existed at all times within the artery (Beaujeu, 1963). He similarly demonstrated the presence of blood in the left ventricle during a vivisection experiment on an animal, in which he punctured the animal's left ventricle (Rothschuh, 1973). While conceding that it was not possible for an internal fire to reside in a blood-filled left ventricle, Galen still maintained that some sort of innate heat emanated from the heart. Proof of this innate cardiac heat lay in the observation that if a limb were bandaged tightly enough, it would lose its pulse as it became cold and pale. When the bandage was released, the pulse would be restored and heat would return to the arm (Fulton & Wilson, 1966). The distribution of this innate heat throughout the body continued to be a major role of the arterial pulse in Galen's physiology.

In order to reconcile his findings with the long-held belief that bodily distribution of *pneuma* is required for life, Galen proposed that the arteries mixed both *pneuma* and blood within their lumen. He thought that the mechanism in which this mixing occurred also lay in the rhythmic dilation and contraction of the heart and arteries. By dilating and enlarging their lumen, the arteries created a vacuum in which venous blood could be pulled into the arteries and in which *pneuma* could be suctioned into the arteries by passing through minute pores in the skin (Fulton & Wilson, 1966). Reciprocal contraction of the arteries would reverse the movement of blood and *pneuma*. This palpable pulse originated from the heart, which Galen demonstrated by tying an isolated artery and showing that no pulse-wave existed distal to the tied knot. Galen then attached a tube to the artery and demonstrated that the pulse-wave was propagated through the tube (Beaujeu, 1963). These ideas represent the first cohesive hypothesis in which heart contractions and arterial pulses were intimately related, and the movement of bodily fluids was driven by contractile instead of thermodynamic forces.

Galen, however, was not convinced that the presence of arterial blood could be explained by suction pull from venous blood via arterial dilation alone, and therefore borrowed Erasistratus's idea of *synanastomoses*. Like Erasistratus, he envisioned that blood flow began in the liver, where all blood was produced with the help of a hepatic innate heat (Rothschuh, 1973). Some of the blood flowed directly from the liver to other organs via the venous system, while the rest of the blood flowed to the right ventricle via the vena cava. At the level of the right ventricle, most of the blood flowed through *synanastomoses* located in the interventricular septum and into the left ventricle, where it would mix with *pneuma* and the cardiac innate heat (Rothschuh, 1973). Blood not traveling through the interventricular septum would pass through the pulmonary artery to nourish the lungs. Galen conceded that collapse of the lung during expiration might push some blood from the lungs into the pulmonary vein via pulmonary s*ynanastomoses*, but the amount of blood that traveled this route was minuscule compared to the amount traveling through the interventricular septum (Fulton & Wilson, 1966). Galen was therefore tantalizingly close to deducing pulmonary circulation, and from that intellectual standpoint the possibility of unidirectional circulation. That discovery would not occur for another fifteen centuries.

CONCLUSION

The unidirectional circulation of blood from the heart through pulmonary and systemic vasculatures and back to the heart would not be advocated until 1628 CE, when William Harvey published his treatise *Exercitatio Anatomica de Motu Cordis et Sanguinis* (*On the Motion of the Heart and Blood*). This discovery set the stage for a radical reconceptualizing of all organs and their functions, particularly the nature of the heart and the liver, and the origin of internal heat. From this seminal discovery, the field of cardiology and vascular medicine has since witnessed astounding achievements beyond what any physician of antiquity could possibly have imagined: cardiac electrophysiology, interventional cardiology, and even epigenetic associations with cardiac disease. But in reviewing what our ancient predecessors believed and how they came to their conclusions, we should remember that any and all future intellectual breakthroughs will depend on the same skill set that the physicians in antiquity possessed: deductive reasoning, free of preconceived assumptions, that is applied to objective, reproducible observations.

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Conflict of Interest Disclosure
The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. No conflicts were noted.

Acknowledgments
The author would like to thank the staff of the D. Samuel Gottesman Library at Albert Einstein College of Medicine and the staff of the New York Public Library for their support in this endeavor.

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Drug Discovery over the Past Thirty Years: Why Aren't There More New Drugs?

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The rate of drug discovery has not kept pace with the exponential increase in biomedical knowledge. For the past 30 years, the number of new molecular entities approved by the United States Food and Drug Administration has averaged 20 to 30 drugs per year, except for a peak in the mid-1990s that briefly doubled this rate. This modest productivity cannot be explained by lack of funding, as the research budgets of government- and industry-funded programs have increased threefold to fivefold over the past three decades. Various arguments have been proposed to account for the relative lack of innovative new drugs, but little consideration has been given to the focus on hypothesis-driven translational research. In theory, the emphasis on translational research should have led to an increase in the number of new drugs. However, in considering the historical perspective of drug discovery and the role of serendipity, it can be argued that the emphasis on translational research diverts scientists from pursuing basic-science studies that give rise to fundamental discoveries. In many cases, retro-translational research (from clinic to basic science) is necessary before the disease process can be understood well enough for scientists to develop therapeutics. Ultimately, a balance of disease-oriented and basic-science research on fundamental processes is optimal.

The pace of drug discovery paralleled the pace of science in general for most of the 1900s. As more was learned about the basic principles of biology and the molecular basis of disease, it became easier to develop rational medicines to treat diseases. At least in theory. In practice, most drug discoveries were based on random chance, or to use a nicer-sounding word, serendipity. A classic example is that of penicillin—a paradigm-shifting drug discovered by a chance observation of lysed bacteria on a culture dish by Alexander Fleming (although technically the discovery of penicillin was made decades earlier by Ernest Duchesne, a medical student who never published his discovery except in his thesis). There are many other examples of drugs discovered by chance, and these far outnumber the drugs that were developed by rational design.

The general strategy for rationally designing a drug involves identifying a target and developing a molecule that binds to the target and affects its properties in the desired way. Then the molecule is optimized for drug like properties (nontoxic; good absorption and distribution). A classic example is that of angiotensin converting enzyme (ACE) inhibitors, rationally designed to block ACE activity and reduce hypertension. There are other examples of drugs that were rationally designed, but in most cases the story had a bit of a twist. For example, sildenafil was rationally developed as an inhibitor of cGMP-specific phosphodiesterase-5, with the idea that it would be useful for treating hypertension and angina pectoris. During clinical trials men given the drug reported a pleasurable side effect, and Pfizer ended up marketing the drug for erectile dysfunction rather than for the originally intended application.

Another classic example of rational drug design is sumatriptan, an antimigraine drug approved by the Food and Drug Administration (FDA) in 1991. This drug was developed as an agonist of serotonin 5HT-1b and 1d receptors; activation of these receptors was known to lead to vasoconstriction, which was thought to be beneficial for treating migraine headaches. The drug worked well in clinical trials and has been a major advance in the treatment of migraines. But while the mechanism of the drug is still thought to involve serotonin receptors, the original idea has been questioned. The current hypothesis is that sumatriptan and related drugs prevent the secretion of inflammatory peptides such as calcitonin gene-related peptide. Therefore, the original concept that led to the drug's development may have been wrong, but useful drugs were ultimately developed.

FUNDING FOR BIOMEDICAL RESEARCH AND DRUG DISCOVERY

During the 1970s and early 1980s, there were only modest increases each year in the amount of money spent by drug companies for research and development (Figure 1). Similarly, when adjusted for inflation the total budget of the National Institutes of Health (NIH) showed small yearly increases or decreases during this period. Since 1982, both the NIH budget and pharmaceutical company research expenditures rapidly rose from $8 billion to between $30 billion and $50 billion (all numbers are inflation-adjusted to 2012); this represents a three- to fivefold increase. If drug development were proceeding on par with scientific discoveries, we would be adding significantly more and more drugs each year. But except for a surge of new drugs in the mid-1990s, the average rate of FDA approval of new molecular entities is only 20 to 30 per year (Figure 1). Counting only new molecular entities means each drug is counted only once, when it is approved for the first time; this excludes older drugs that were reformulated, which

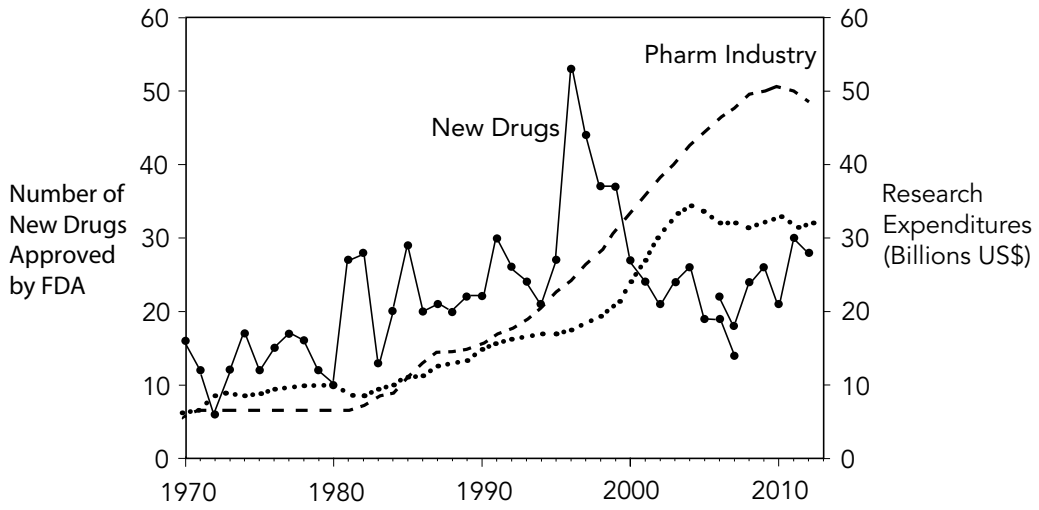

Figure 1 | Drug development and research expenditures from 1970 to 2012. Circles and left axis show the number of new molecular entities approved by the FDA each year; these include compounds from new drug applications as well as biologicals from biologics license applications to the FDA. The 1970–2007 data are from *Goodman and Gilman's The Pharmacological Basis of Therapeutics* and the 2006–2012 data are from the FDA website (www.fda.gov); the two sources give slightly different numbers for the two years of overlap. Squares and right axis show research and development costs of the U.S.-based pharmaceutical industry; the 1970–2007 data are from *Goodman and Gilman's The Pharmacological Basis of Therapeutics* and the 2007–2012 data are from the Pharmaceutical Research and Manufacturers of America website (www.phrma.org). Diamonds and right axis show the total NIH budget, of which the majority represents the extramural and intramural research programs. Increased money for the NIH from the American Recovery & Reinvestment Act of 2009 is not included. Both pharmaceutical industry expenditures and the NIH budget are in billions of U.S. dollars and are adjusted for inflation to 2012 using the U.S. Bureau of Labor Statistics consumer price index adjustment website (http://www.bls.gov/cpi/).

requires FDA approval, as well as older drugs for which new uses were discovered and approved.

From 1970 through 1996 (Figure 1), the rate of new-drug discovery generally parallels the amount of research money, even though there is a time lag between basic research and the approval of a drug by the FDA. Extrapolating from the plot of drug approvals per year from this time period, one would have predicted that in 2012 there would be 50 to 100 new drugs approved. However, the period from 1996 through 2006 shows the opposite trend: a falling rate of drug approval while research expenditures dramatically rise. Extrapolating from this time period, one would predict that fewer than five new drugs would have been approved in 2012. When the number of new drugs approved over the past five years is included in the analysis, it appears that there has been a steady state of 20 to 30 drug approvals per year for the past 30 years, except for a brief increase in the mid-1990s. Clearly, the number of new drug approvals hasn't risen to more than 50 or shrunk to fewer than five. But shouldn't there be many more new drugs when one considers the three- to fivefold increase in research funding?

IS THE PROBLEM WITH THE APPROVAL PROCESS?

One possibility to consider is that the problem has been the approval process, not the actual development of drugs. It is conceivable that many new drugs were developed in recent years but didn't make it through the FDA approval process. A related possibility is that the drug companies were more rigorous in their screening, and prevented unsafe drugs from being put into the pipeline and marketed. However, both of these possibilities are unlikely to account for the lack of correlation between drug approval and research expenditures. The ratio of drugs approved by the FDA to all submissions for new drug applications has remained relatively constant. The FDA has blocked the approval of some drugs. For example, rimonabant is a CB1 cannabinoid receptor antagonist that produces modest weight loss. The drug was approved in 2006 in Europe but not approved by the FDA because of safety concerns. Rimonabant was withdrawn from the European market in 2009 due to adverse events. Before it was withdrawn, some people argued that the FDA was too restrictive, preventing a useful drug from being marketed. After the side effects emerged, the FDA was lauded for protecting the population. Some people claim that the FDA is erring on the side of approving too many drugs, in part because of a 1992 law that charges drug companies money to offset the cost of the approval process. The purpose of this law, the Prescription Drug User Fee Act, was to shorten the time it takes for the FDA to evaluate drugs and reduce its large backlog by allowing the hiring of more personnel. This law may have contributed to the increase in approved drugs in the mid-1990s, although it has been argued that this was not a contributing factor (Graham, 2005). Regardless of what caused the spike in approvals in the mid-1990s, the fraction of requests approved by the FDA has not changed dramatically over

the past few decades, suggesting that other factors are the major contributors to the limited number of new drugs.

The other related possibility—that drug companies are doing a better job of avoiding potentially unsafe drugs—may be partially correct, as there are improved methods of predicting toxicities of drugs and their metabolites. However, it is unlikely that this is a major contributor to the dearth of new drugs, for two reasons. First, the number of drugs withdrawn from the market due to toxicities is rather small; only 3% of the drugs approved over the period from 1975 to 2000 were later withdrawn (Lasser et al., 2002). A larger fraction (8%) of the drugs approved during this period required new black-box warnings after marketing, indicating additional toxicities that were not known at the time of approval, but these drugs have remained on the market. Although higher than one would hope, the 3% rate for drug withdrawal is so small that if companies had somehow figured out how to avoid marketing such drugs, the number of new drugs would decrease by only one drug per year (at the current rate of approximately 30 new drugs per year). Second, companies do not seem to have figured out how to avoid marketing toxic drugs. In the past decade, a number of approved drugs have been withdrawn from the market—rofecoxib (Vioxx), tegaserod (Zelnorm), and sibutramine (Meridia), just to name a few. It would be hard to argue that drug companies are holding back drugs because of toxicities; they seem to withdraw drugs only when faced with overwhelming evidence of adverse reactions.

DRUGS NOT DEVELOPED

Because the drug-approval process does not appear to be the major reason for the small number of new drugs relative to the amount of money spent, it appears that fewer drugs were developed per dollar spent (even when adjusted for inflation). This may be for one of two reasons: money was spent on the right things, but it takes more money now to develop drugs, or money was not spent on the right things. The popular answer among scientists I have consulted is the first: that research in general is much more expensive than it was in the past, even when costs are adjusted for inflation. While this may be true for clinical research, the cost of most basic research is higher only because we can accomplish so much more with current techniques. For example, DNA sequencing used to be done manually in the early 1980s, and a single person working full time could sequence several kilobases in a year. With the current generation of DNA-sequencing instruments, a single person can accomplish this much in a fraction of a second. In the past decade the cost of sequencing a million bases of DNA has dropped from thousands of dollars to under 10 cents (http://www.genome.gov/sequencingcosts/). And it's not just DNA sequencing that has gotten cheaper; advances in many other techniques have also lowered the cost of science by allowing much more to be accomplished in the same amount of time. When looking at the cost per experiment, yes—the costs have gone up for most things. But when considering the cost relative to the amount and quality of data, there has definitely been a cost reduction in nearly all fields of basic research. Large amounts of information are available for free on the Internet, further reducing the overall cost of science.

Another explanation for the high cost of drug discovery is that many of the easy problems have been solved, and the remaining problems are more complex: neurodegeneration, dementia, and obesity, to name a few. But many of the disorders that are often treatable with drugs are also complex: schizophrenia, depression, and epilepsy, for example. How were drugs for treating these disorders found? The short answer is serendipity. The first drug for treating schizophrenia (chlorpromazine) was developed as an antihistamine, and, like many first-generation drugs in this class, was highly sedating. For this reason, it was tested as a sedative to calm highly agitated schizophrenics, and it worked. But what was significant was that, after several weeks of treatment, the underlying symptoms resolved in some of the patients—the voices in their heads were quieted. This drug was clearly doing something that other antihistamines were not, and further research uncovered the dopamine D2 receptor-blocking properties of chlorpromazine, leading to a number of additional antischizophrenic drugs. The discovery of the first antidepressant also involved a large amount of luck. The drug iproniazid was being tested in patients with tuberculosis; it was being compared to the related molecule isoniazid, which had been developed earlier for this disease. The derivative drug also worked for tuberculosis, but in addition seemed to lift the mood of the patients more than what would be expected if the tuberculosis were cured. (Because this disease was often deadly, the curing of the tuberculosis was equivalent to being pardoned from death row, which would certainly improve one's mood.) Because iproniazid was even more effective than isoniazid at making patients happy, the properties of the two drugs were studied, and iproniazid was found to inhibit monoamine oxidase (MAO). This led to many additional MAO inhibitors, some of which are still used today (although they are not frontline therapy).

TRANSLATIONAL VERSUS BASIC RESEARCH

The final possibility to consider is that the relative dearth of new drugs is due to money being spent on the wrong things. But more money than ever has been going into translational research—shouldn't this be leading to more drugs? How could this be the problem?

The term "translational research" was virtually nonexistent prior to the early 1970s (except to refer to the translation of RNA into protein); it has now become commonplace in the literature and funded NIH grants (Figure 2). Although the NIH doesn't break out the dollar amounts for applied and translational research versus basic research, it has been estimated that 41% of the NIH budget was for applied research in 2007, and this increased to 46% in 2010 (http://www.biocentury.com/promotions/ budgetfight/us-budget-fight-over-basic-translational-research-spending-by-nih-a1.

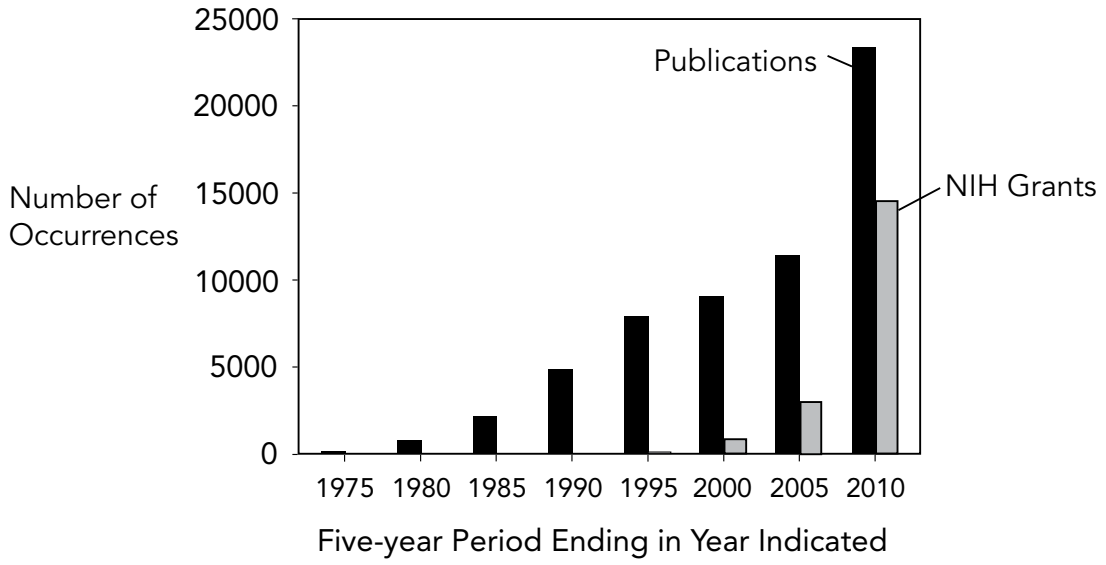

Figure 2 | Appearance of the term "translational research" in publications and research grants from 1971 to 2010. Searches for the term (in quotes) were performed in PubMed (http://www.ncbi.nlm.nih.gov) and the NIH Reporter (http://projectreporter.nih.gov/reporter.cfm) over the indicated five-year period.

htm). In addition to the large amount of money spent on translational research through existing funding channels, in 2012 the NIH launched a new $575 million National Center for Advancing Translational Sciences.

Given the long history of serendipity in drug discovery, it is somewhat surprising that the current approach to drug development largely ignores it, focusing instead on rational drug design and translational research. It is possible that the intense focus on these areas is exactly the reason for the relative lack of new drugs. Translational research is a one-way street to the clinic. But if one doesn't have a good sense of the basic science, it is impossible to know what is best to translate. An excellent example of this is the discovery that penicillin mold had antibiotic properties, which was made by Ernest Duchesne in 1896. Even though Duchesne had found that penicillin extracts could save the lives of animals infected with toxic amounts of bacteria, it was not considered appropriate for treating humans because the hypothesized mechanism was incorrect—the mold was thought to outcompete the bacteria in a struggle for resources, rather than to secrete an antibiotic substance that could be useful as a drug. When Alexander Fleming rediscovered penicillin several decades later, in 1928, he also misidentified the mechanism and thought it functioned like lysozyme, a bactericidal enzyme he had discovered in 1923. Enzymes do not make good drugs, and partly for this reason (along with the difficulty of mass-producing the penicillin extract), it took more than a decade before the extract was tested in animals and found to be effective.

Fortunately, the role of serendipity in the drug-discovery process has been recognized; the NIH and several major pharmaceutical companies have a pilot project to allow scientists in academia to test potential drugs for additional uses ("NIH Unveils Plan," 2012). For the most part, the drugs made available through this program are compounds that were being developed for one purpose, did well in animal studies and phase I human clinical trials, but didn't work so well in the efficacy trials in phase II or III testing. As a result, these haven't been approved by the FDA for marketing, and the companies are eager to find a use (especially one with a lucrative market) for them.

BASIC SCIENCE AND RETRO-TRANSLATIONAL RESEARCH

While the program aimed at finding new uses for compounds already developed is likely to yield some new drugs, there is still a need for more basic research. In times of flat NIH budgets, increased funding for translational research means that there is less funding for basic research. But without a better understanding of the fundamental biology that underlies them, it is not possible to understand disease processes. Little is known about the function of a large fraction of the 20,000 or so human genes, and even well-studied genes and their gene products are far from being understood. For example, tubulin has been known for decades, and a search of PubMed pulls up over 22,000 articles on tubulin. A large number of post-translational modifications of tubulin are known to occur, but the precise molecular forms of tubulin and the functions of each form are not known. Thus, even well-studied genes and gene products are not fully understood, and basic science in these areas may reveal novel targets for drugs. But drug development should not be the main objective of pure basic science aimed at understanding the role of each gene or gene product. Simply learning more about a biological process should be sufficient reason to study something; this

was the common sentiment in the 1970s and 1980s, before the subsequent focus on translational research.

Another area that is likely to enhance drug development is retro-translational research—from clinic (or animal model) toward basic science—to better understand the underlying biology so that the best treatment can be designed. Although the term "retro-translational research" is relatively new, the concept is old. This was the approach used to figure out how chlorpromazine, iproniazid, and many other drugs produced their unexpected results, an approach that ultimately led to breakthroughs in the treatment of schizophrenia, depression, and other disorders. If Duchesne had taken this approach with penicillin, he likely would have realized its amazing potential and been able to interest companies in developing this lifesaving drug decades before Howard Florey, Ernst Chain, and others developed Fleming's penicillin in the 1930s. Collectively, translational and retro-translational research can be considered disease-oriented research, allowing a two-way street, from basic science to the clinic and back, to be traveled several times before the system is exploited and a drug is developed (if such a drug is possible; not all research is bound to lead to drug development).

CONCLUSION

At some point, the majority of new drugs may be rationally designed based on knowledge of disease processes, underlying biology and biochemistry, and translational research. Up to now, serendipity and retro-translational research have played a much larger role than rational design. The relatively constant number of new drugs approved each year over the past 30 years, despite the great increase in funding, may be due to the emphasis on translational and applied science rather than on basic research.

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Conflict of Interest Disclosure

The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. No conflicts were noted.

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Dr. Richard M. Hays – An Einstein Legend If There Ever Was

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My first memory of Dr. Richard Hays is of him sitting on the stage of Robbins auditorium delivering a lecture on renal physiology. At that time, I did not realize that medicine could be taught with such kindness and compassion. A majority of my class did not go into nephrology, but we all loved him as a teacher. He regarded students highly, and would listen to their every interest with the seriousness that one would grant any renowned scientist. He understood and practiced the idea that curiosity kept your mind and heart young. For that reason, I had always felt that Dr. Hays harbored an uncanny youth about him, and wished to catch a bit of it when he was around.

One quality no one can deny Dr. Hays is his persistence. He was especially dedicated to causes he thought would benefit Einstein, an institution he held dear to his heart. One such example was how hard he fought to keep a close relationship between the Albert Einstein College of Medicine and Jacobi Medical Center. For non-academic reasons, this relationship was weakened and resulted in the break-up of the renal division that he led for 9 years. He had fought tirelessly to bring them back together despite administrative obstacles. We loved that he never gave up, even when we did.

In many ways, Dr. Hays was a renaissance man. You could not find a soul more interested in life and living. He was a poet, gracing every family occasion with an original poem. He was a musician, complementing his warm home of a lovely wife and four exceptional children with singing and instrument playing. He was an athlete, leading his high school football team as captain, and had a short (very short) career boxing when he served in the Army Air Force. And of course he was a physician-scientist.

His academic career that would eventually lead him to the field of medicine began at distinguished institutions. He studied at Harvard College and majored in anthropology as an undergraduate student. This was followed by his medical school education at the Columbia College of Physicians and Surgeons where he first became intrigued by the physiology of the kidney. His residency in Internal Medicine was completed at Beth Israel Hospital in Boston. His two fellowships, the first under Dr. William Schwartz at the Tufts-New England Center Hospital, and a very significant second under Dr. Alexander Leaf at the Massachusetts General Hospital launched his scientific career. We were fortunate that he chose to join the Einstein faculty in 1960. In the following two decades, Dr. Hays published ground-

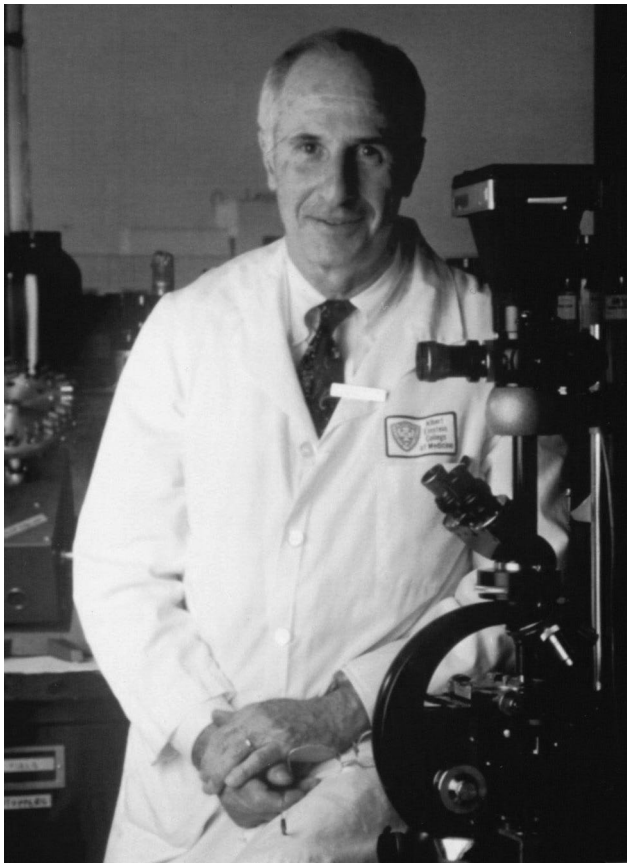

Figure 1 | Richard M. Hays, MD.

breaking research on mechanisms of osmotic water flow that would eventually lead to the discovery of aquaporins. He continued to ponder over water and sodium disorders throughout his career and into retirement. To that end, he devoted much of his time and passion to the Mount Desert Island Biological Laboratory in Maine, a place that embraces the bold missions of promoting research and education in marine organisms, fostering an understanding of the environment, while advancing human health. He joined the Laboratory as a medical student in 1952, and became its Director from 1976-1978.

Towards the latter half of Dr. Hays' career, he focused on medical education. Constantly rethinking how we teach students, he even founded the Division of Education at Einstein. He was not afraid of change and the struggles that may come with them. Empowering students to teach not only themselves but the faculty was a goal of his. Once

more, he treated students with the respect that is not always so visible in our traditional educational hierarchy. Not surprisingly, he was lauded with teaching awards year after year. Dr. Hays was inducted in the Leo M. Davidoff Society in 1995 and received its Lifetime Achievement Award for Outstanding Teaching in 2003.

What will be the legacy of Dr. Hays? Will it be that of a beloved teacher, a committed scientist, or a devoted family man? Will it be of an activist, fighting the powers-that-be for ideas that he firmly believed in? The answer is undoubtedly different for every person. I remember Dr. Hays as a man who embodies the best of human character. He was a force of nature with the deepest heart and the utmost integrity. I remember Dr. Hays as someone whom I wish to aspire to. If I can live the way he lived and love the way he loved, I cannot and will not ask for more. I remember Dr. Hays as the figure on the stage of Robbins auditorium sitting so invitingly as he introduced the world of nephrology to a group of bewildered students, and I miss him dearly.

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Conflict of Interest Disclosures
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Memorial Eulogy for Dr. Sharon Silbiger

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I was a close colleague of Sharon's at work for almost 25 years. It was an honor to know her, and I am deeply honored to be able to speak about her today.

In the last three days, I've received many emails about Sharon, from her students, former residents, and colleagues, many of whom are here today. Each of you remembers Sharon in your own way. I'll do my best to honor each of your memories.

She had a remarkable career.

During her senior year of medical school, she worked at a medical clinic in a refugee camp in Thailand. This was an early indicator of her strong sense of social justice, which played out later in her decision to care for patients, not of affluence, but patients of poverty and disadvantage, in the Bronx.

She became a kidney specialist, a nephrologist, and joined the nephrology division of Albert Einstein College of Medicine and Montefiore Medical Center in 1988, at about the same time that I joined the same division.

Our mutual close colleague, Detlef Schlondorff, wrote to me a few days ago: "She was a real New Yorker, straight forward, to the point, no nonsense, honest..."

Indeed. I remember first meeting Sharon, in the Moses 2 conference room. We were conversing, and I must have said something a little aggressive, and she pushed back. I pushed back at her, and she pushed back at me. After a couple more rounds of this, she held up her hand and said "Vic, try to be nice. You *need* friends." Sage advice which, to this day, I tell to others, and to myself.

She quickly established herself as an outstanding physician, teacher, and scientist. In her research, she worked closely with Joel Neugarten on the question of why men with kidney disease more often progress to the point of needing dialysis or transplantation, compared to women.

In a series of important laboratory experiments, Sharon and Joel showed that a woman's estrogen protects the kidney's filtering unit from damage. Their scientific studies are required reading for all nephrologists.

In part because these studies made her an expert on gender, and in part because she was a natural leader, Sharon became president of a national organization called Women in Nephrology, which advances the careers of women in the field. The current president of the organization, who is at the Mayo Clinic, wrote to me: "Sharon was a wonderful, strong person, and a dear friend and mentor to me, as well as to a large army of women."

About a decade ago, Sharon took on the job of directing our large and complex Internal Medicine training program. She and I spent many early mornings together, giving back-to-back presentations to those medical students who were applying to our program. Sharon would first warm up the crowd with some light banter and jokes about how the black suit worn for interview days will grow tiresome, and how the applicants' parents must be nervous because their children are interviewing in "the Bronx". It was good standup comedy. Then I would give a rather dry slide show, which she sat through, morning after morning. We used to say we could give each other's talks from memory, which was true.

Over the course of her eight years in this position, Sharon's program trained nearly 700 residents. Despite the large size of the program, Sharon made each resident feel special. She was the ultimate good and loving parent. Doctors in training get exhausted, they make mistakes, they lose their way, they sometimes act out. Sharon listened, gave sound advice, and offered a shoulder to cry on. Occasionally - because she had to - she admonished, or even placed a resident on probation. But always, there was a warm hug or a pat on the back.

She set very high standards for patient care with her trainees. Vafa Tabatabaie, who was a resident under Sharon, wrote to me that her most vivid memory of Sharon is the speech she would give to the new interns on orientation day. Vafa remembered Sharon's speech this way:

"You admitted an IV drug user with endocarditis, you begged the PICC line nurse for two days because you couldn't find a single tiny vein, you fought with the ID fellow to get antibiotic approval, and you finally managed to discharge the patient after 23 days in the hospital; now the patient is readmitted to you after one week outside the hospital, with his second episode of endocarditis, because he injected heroin with the same dirty needle. You feel so frustrated that you want to scream and run out and resign and become a pole dancer. But always remember, it's not about you. It's about him. You will leave the hospital tomorrow, but these patients won't."

Three years ago, Sharon moved over to the medical school and became the director of Internal Medicine education for all 3rd and 4th year Einstein medical students.

She brought her same strong parenting skills to this task. Medical students applying for internships have to write a

"personal statement." Sharon would edit these with each student, making sure the statements told a good story and were interesting enough to stand out. But she also made sure they weren't *so* interesting as to seem weird, which would jeopardize the student's chances.

She counseled the students as to which internships would be a good fit, adjusting her advice to their individual strengths and weaknesses. She told them how she had initially started out in Neurology, but had changed to Internal Medicine, so if they were confused or uncertain about their career choice, they should remember that nothing is irreversible, and it will all work out fine. This past spring, under Sharon's guidance, more Einstein graduates got into more prestigious internships than at any time in memory.

Asked some months ago to be the keynote speaker at an important Einstein student event, she realized she might not be well enough to attend in person. So in typical Sharon style, she re-conceptualized the presentation and, instead of delivering a stand-up speech, she had the College of Medicine make a video, which included both patients talking about what they want in a doctor, and Sharon's residents talking about the rewards of becoming a doctor. It was novel, and it was incredibly moving, even without knowing of Sharon's condition. But of course, Sharon was there in the video also, urging on the students, in her role both as professor and patient.

In another display of resourcefulness, she once intended to send a negative email about a boss to a colleague but, by accident, sent it to the boss himself. Most of us would panic after we realized we'd hit the "send" button. Not Sharon. She simply enlisted the boss's secretary, whom she had befriended, to go in and delete the offending email from the boss's "in" box. No problem.

A child of two holocaust survivors, Sharon was impressively tough in the face of adversity, and she seemed to get only tougher as the going got harder. At our residency graduation ceremonies each spring, Sharon would present various awards to the graduates. One of these, the Barry Mishkin Award, is for humanism, and is named after a wonderful resident who died during his training with us. Sharon had known and loved Barry, and year after year, when she presented this particular award, she choked up.

But, at graduation in the spring of 2010, she didn't choke up. This was the first graduation she attended after her diagnosis, her pelvic and hip surgery, rehab, and other therapies. She was composed and dry-eyed. After she sat down next to me, I leaned over and said "Sharon, you've toughened up." In typical Sharon style, all she said was "Yup."

A former resident wrote to me that she had run into Sharon in the hospital hallway at some point after Sharon had been through her surgery and was using a cane. Yet, the whole conversation was about the resident's marital problems. Sharon said nothing of her own travails and, in fact, simply ended the conversation with "Isn't life interesting?"

A faculty member wrote that she had met Sharon using her cane, and had inquired if she had a leg injury. Sharon simply said, "It's a long story."

She came in to work as long as she physically could, meeting with students, organizing dinner parties for departing faculty members, moving forward our plans for a new dialysis center.

When she became too ill to come into the office, we would meet in her apartment where, among the other items on her work agenda, she pushed me - to be honest before I was ready - pushed me to find a successor for her at Einstein, so that her students wouldn't be short-changed.

And always, she talked about Jonah. For all her career accomplishments, *Jonah* was the *center* of her universe. She talked about how much she loved him, and how she had done her utmost to make sure he would be all right.

She talked about her husband Alan, her partner and true friend. She saw his inner strengths, and knew that he'll be all right, too.

She spoke with love and gratitude of her mother and her sister, with whom she had shared so much, and who cared for her so lovingly, through to the end.

We're approaching the Jewish New Year. A short story by the Yiddish writer I. L Peretz tells of a Hasidic rabbi in a Russian shtetl who disappears every year during the Days of Awe. His Hasidic followers claim that, during those days, the rabbi ascends to heaven to plead with God on their behalf. A skeptic in the village sets out to disprove this belief, and at the next Rosh Hashanah, hides himself under the rabbi's bed to spy on him. The skeptic finds that, in fact, the rabbi disguises himself as a Russian peasant, goes into the woods, chops down a tree with an axe, takes the bundle of wood to the broken-down shack of a sick, old woman, pretends to be Vasil, a peasant, and makes a fire in the oven. And as he puts each stick of wood into the oven, he recites a part of the day's penitential prayers.

After witnessing this anonymous act of charity, the skeptic becomes a disciple of the rabbi, and thereafter, whenever he hears a Hasid mention that "during the Ten Days of Penitence the rabbi of Nemirov goes up to heaven", the skeptic adds quietly, "if not higher."

Many will say that Sharon Silbiger has ascended into heaven. I would only add: "if not higher."

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Editor's Note: Adapter from the 2012 Memorial Eulogy for Dr. Silbiger delivered by Dr. Schuster.

Memorial Eulogy for Dr. Richard M. Hays

Victor L. Schuster, MD
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It's an honor for me to speak today about Dr. Hays and his career at Albert Einstein College of Medicine.

Dick attended college at Harvard and medical school at Columbia University. He then took further training in kidney research at Harvard's teaching hospitals, before joining the Einstein faculty in 1960.

At Einstein, Dick was a scientist, physician, and teacher. He was also known for having a good sense of humor, an infectious chuckle, and a commitment to excellence.

As to his science, the big picture is that he was a naturalist in the tradition of Charles Darwin, by which I mean he was a keen observer of nature and species and organisms.

This began early. As an undergraduate, he majored in anthropology. the science of humanity. Thus, the first species he observed as a naturalist was his fellow human beings, *Homo sapiens*.

The first species Dick studied *experimentally* was the harbor seal, *Phoca vitulina*. This occurred because, while still a medical student, Dick was invited one summer to the Mount Desert Island Biological Laboratory, in Salisbury Cove, Maine, to work on what is called the "diving reflex" in the seal.

It's fitting that Dick's first exposure to research took place at Mount Desert, a famous and important research lab, because he later became its lab director and was a lifelong ardent supporter.

His writing about that first summer research experience gives you a feeling for the man:

"So, up we went: Stan Bradley, Paul Marks, Willoughby Latham and others, to study the diving reflex. I couldn't wait to assist in the experiment. On the appointed day the seal was wheeled into our lab on a cart. He was one angry subject, and Stan warned me to stay away from his mouth, which had teeth as sharp as a dog's. At one point in the experiment a funnel would be clamped over the seal's nose to simulate a dive. I was given a bucket, and stationed at the distal end of the seal. Ever inquisitive, I asked what the bucket was for, and Stan said: "you'll see". The experiment began, and soon enough the funnel was placed over the seal's nose. Voila, the dive had begun! And soon enough, my role became clear, as a massive diarrheal stream emerged from the seal. I deftly caught it in the bucket, and my scientific career had begun."

Like any good naturalist, Dick studied many different species, including the tadpole of the green toad, *Bufo viridis*, the mud shark, *Squalus acanthius*, and the winter flounder, *Pseudopleuronectes americanus*.

Dick also knew more than you'd think he would about another species, *Periplaneta americana*, the North American cockroach. Ceci Haas told me that, years ago, she had a strong reaction to her roach-infested office at Einstein, whereupon Dick gave her a book entitled "Archie and Mehitabel". For those of you too young to remember - and this includes me - for many years there was a daily cartoon in the New York Sun featuring a fictional cockroach and alley cat named Archie and Mehitabel. Archie the cockroach typed by jumping from key to key on the typewriter. I can just see the smile on Dick's face as he gave Ceci this treatise on her office cohabitants (I'm happy to report that we no longer have roaches at Einstein).

Dick also knew the laboratory mouse, *Mus musculus*. One morning at Einstein, a renal fellow presented a research paper about a mouse that had been genetically manipulated by scientists to live twice as long as normal. The researchers had dubbed their creation the "Methuselah Mouse". Dick leaned over to me at this point and did a pitch-perfect adaptation of a song from Porgy & Bess:

"But who calls dat livin'
when no gal'll give in,
to no mouse what's 900 years."

But the species Dick studied most was the cane toad, *Bufo marinus*. This toad is native to central and South America, will eat about anything, dead or alive, and is very large; the largest to date weighed 6 pounds and had a 15 inch body length, not counting the legs.

Now, you are probably asking yourself, why on earth would a Harvard-trained physician do experiments on a giant Latino toad? More importantly, why would is this guy telling you about it at Dick's memorial service?

Well, throughout his career, Dick was always trying to figure out how the kidney works. Specifically, every day the kidney generates the equivalent of a 55 gallon drum's worth of what one might call "preliminary urine", almost all of which is, in turn, reabsorbed back into the body, so that we end up excreting only a couple of quarts as final urine.

Now, the kidney is extremely complex and hard to study experimentally, especially with the techniques available to Dick at the time. To make progress on a tough question like this, you need what is called a "model system", that is, a simpler version of the complex thing. But what model

system could there be that would mimic the reabsorption of fluid by the human kidney?

The toad urinary bladder. The toad lives near water, but when the dry season comes, it buries down into the mud. The mud then dries out, but the toad does not, because it has stored water in its urinary bladder and reabsorbs it as needed during the dry spell.

Dick and his mentor, Alex Leaf, cleverly reasoned that the cellular machinery used by the toad to reabsorb water from its bladder might be similar to that used by the human kidney to reabsorb much of what I'm calling here "preliminary urine".

In a landmark paper, they showed that a hormone called vasopressin, which is the same hormone in man and toad, stimulates this water reabsorption by the toad bladder. This was a crucial finding in kidney research; we now know a tremendous amount about the kidney, and the part about vasopressin and water reabsorption is very, very important, and it all builds upon that initial finding in the toad bladder by Hays & Leaf.

Moreover, based on subsequent experiments, Hays and Leaf proposed that the reabsorbed water moves through the bladder wall by way of water channels. This proposal was quite controversial. But Dick's lab at Einstein pursued this question, and showed both that water channels exist, and that vasopressin increases their number.

Fast forward to twenty years ago: a scientist named Peter Agre at Johns Hopkins discovers a new gene whose function is unknown. Based on Dick's work, Dr. Agre hypothesizes that his new gene might encode a water channel. It turns out to be true, and in 2003 Agre wins the Nobel Prize for this finding. We now know that there are many varieties of these water channels, and they're important in many different cellular processes, in the eye, the brain, and other organs. All this, because of Dick Hays and his giant toads.

In addition to his research, Dick was a superb teacher. But more than that, he was a committed leader in medical education.

He directed the kidney course for medical students at Einstein for many years, and the students adored him, seeing him as that wise and good-natured uncle who always has your best interest at heart.

Along with Howard Steinman, Dick led an effort to ensure that Einstein students understand the scientific underpinnings of their patients' diseases.

He was an important figure in the development of case-based learning in the Einstein medical school curriculum. As Liise-anne Pirofski said: "He was a great champion of ideas and discussion, and worked hard to preserve both in the educational process."

He always had a special place in his heart for Jacobi hospital, and its role in teaching our students, and when Jacobi formed its own renal division, Dick was their strongest advocate.

We miss Dick: his science, his teaching, his bedside manner, his humor.

But because of him, our lives and our health have been deeply enriched.

We thank him for all he did for us, as we remember him and try to follow in his footsteps.

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Editor's Note
Adapted from the 2012 Memorial Eulogy for Dr. Hays delivered by Dr. Schuster.

Raising the Dead

MRIs failed to detect any spirit. Sonography
probed for an echo; dead seriousness responded
as the red blood cell count hovered a nanobot
above hopelessly dreary. Topnotch surgeons

injected endorphins, went in there determined
to come up with an optimistic sign. They explored
coronal suture for a cracked smile, found only
fissured frowns. Transcranial magnetic simulation

homed-in the humor zone. Electric stimulation
of both nuclei accumbens turned up zero. They
tickled tarsi and phalanges with feathers, tapped
ulnar ligaments for funny-bone twinge, didn't

get a semblance of mirth. Poking around the ribs
for a giggle, MDs traced the nerve to a punch-line
that could elicit a sidesplitter reflex. The features
remained deadpan, so they elected to administer

an enema. The total bill broke the World Bank
of Records, yet the pulse didn't blip. Desperate
for a breath, the team conferred, unanimously
agreed they had operated on the wrong patient.

Symptoms

I long to hold a strand of light,
and a grave yawns like a hippo.

Bending
to sniff a flower,
I grow rigid as concrete.

I want to dream,
instead see only
the wrinkled flesh of my lust.

I go to honor the ones I love,
and mud fouls my hands.

Tears of sorrow overflow,
when I begin to laugh.

I stretch every ligament of wisdom toward
a branch of knowledge,

unwind every convoluted journey
of weathered understanding
in the orbits of my nerves

to grasp an idea of life—
and a blade of grass cuts me.

The final trace of hope vanishes,
and a spirit flies out
taunting . . . *Let's boogie!*

Biographical Note: Bruce Lader (Bridgesbl@aol.com) is the author of five published volumes of poetry. *Discovering Mortality* (March Street Press, 2005) was a finalist for the 2006 Brockman-Campbell Book Award. His third full-length book, *Fugitive Hope,* is forthcoming from Cervená Barva Press. Winner of the 2010 Left Coast Eisteddfod Poetry Competition, his poems have appeared in *Poetry, Roanoke Review, Poet Lore, Harpur Palate, Confrontation, New Millennium Writings,* and other journals and anthologies. He has received a writer-in-residence fellowship from The Wurlitzer Foundation, and is the Director of Bridges Tutoring, an organization that educates multicultural students. Additional information can be found at www.brucelader.com

THE EINSTEIN JOURNAL OF BIOLOGY AND MEDICINE

SUBMISSION OF MANUSCRIPTS: *The Einstein Journal of Biology and Medicine* publishes two issues per year. To submit a manuscript for consideration, please visit our website **(http://www.einstein.yu.edu/ejbm)** for a detailed set of instructions for authors outlining the requirements and format of *The Einstein Journal of Biology and Medicine*.

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CHANGES OF ADDRESS: Allow six weeks for all changes to become effective. All communications should include both old and new addresses (with zip codes) and should be accompanied by a mailing label from a recent issue.

OFFICE OF PUBLICATION: *The Einstein Journal of Biology and Medicine*, Albert Einstein College of Medicine of Yeshiva University, Jack and Pearl Resnick Campus, 1300 Morris Park Ave., Belfer Building, 804D, Bronx, NY 10461. Telephone: (718) 430-8768; Fax: (718) 430-3073; Email: ejbm@med.einstein.yu.edu. Editorial Assistant: Janine Maietto.

Design and Production: Jeneffer Lee. Graphic Arts Center—Albert Einstein College of Medicine of Yeshiva University.

ISSN: 1559-5501 . Printed in the United States on acid-free paper.

EJBM

THE EINSTEIN JOURNAL OF BIOLOGY AND MEDICINE

Volume 29, Issues 1 & 2, 2013

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