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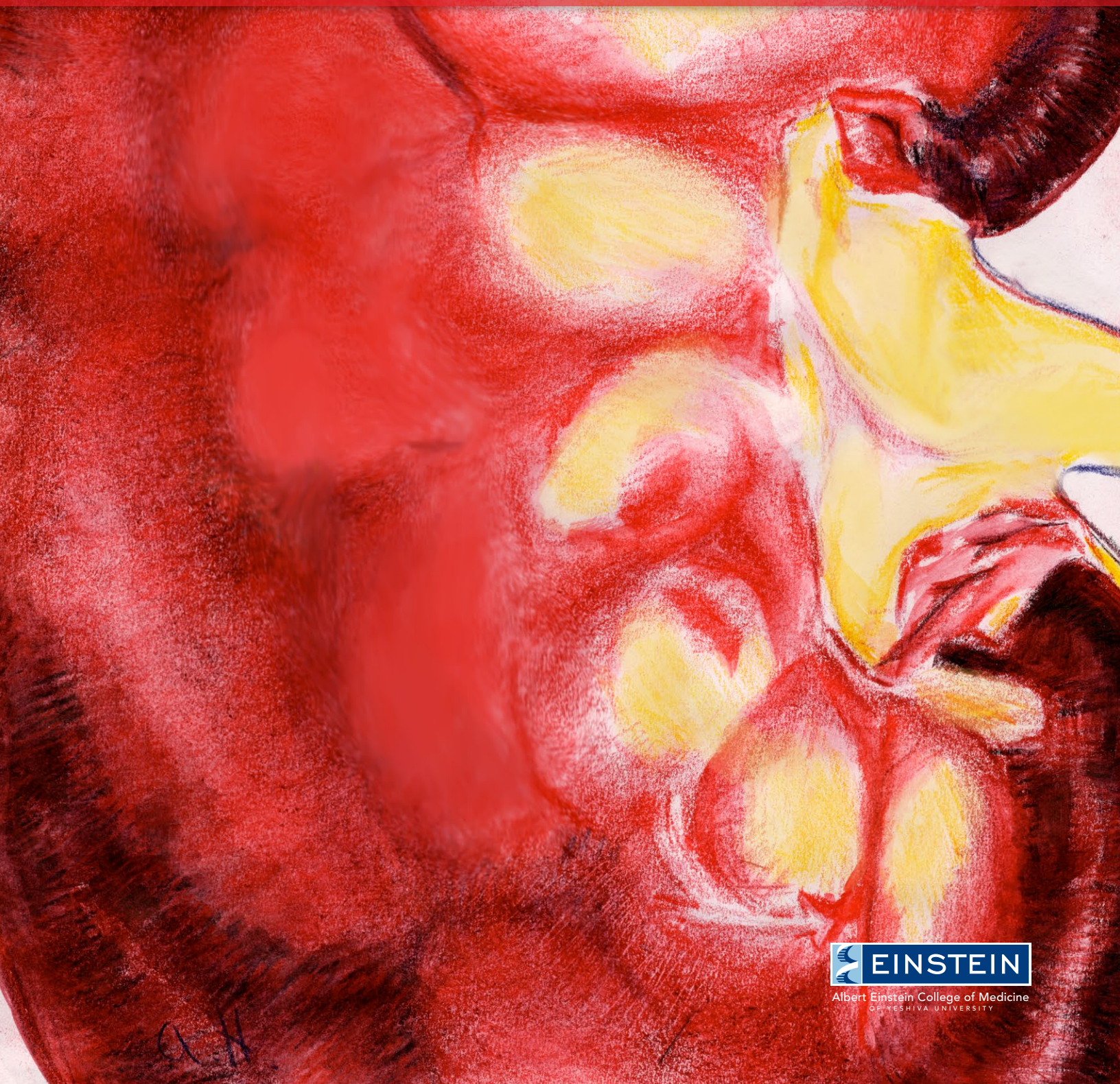

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The *Einstein Journal of Biology and Medicine (EJBM)* is a peer-reviewed general medical scientific journal edited by the students, faculty, and alumni of Albert Einstein College of Medicine. The major purpose of *EJBM* is to serve as a forum for the basic and clinical investigation being conducted by the members and alumni of Albert Einstein College of Medicine as well as other academic, medical, and 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.

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# Inside This Issue





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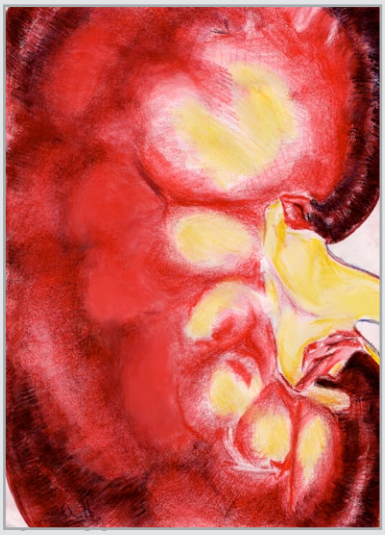

**Renal Anatomy**
*Adina Haramati, 2014.*

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# The Role of the Medical Profession in Swaying Public Policy: Exploring Physician Responsibility and Advocacy

Written by Mark Mikhly with an Afterword by Arthur Ruiz
Edited by Danielle Pasquel and Arthur Ruiz

Physicians in training have a broad range of subjects they must study and in which they must train and develop proficiency. The scope of a doctor's expertise, however, must not be limited to an immediate practical knowledge of anatomical structures or the pathology of a given disease. As medical advances accelerate, physicians are increasingly being called upon not simply to practice medicine in a one-on-one relationship with a patient, but to provide a voice of professional and scientific authority in informing the public about the nature and value of medical developments. In this article, we explore the underpinnings of the physician's authority and the evolution of the relationship between the physician and society, and touch upon contemporary social issues within the purview of physician advocacy. We also consider important questions that arise from that evolving relationship: What are acceptable topics on which a physician may offer a professional opinion? How does a doctor disentangle his or her personal and professional views on a contentious topic? Can a physician ethically "speak for the profession" if there is no medical consensus on a given topic?

## FOUNDATIONS OF PHYSICIAN AUTHORITY: LEGITIMACY AND DEPENDENCE

Medicine in the United States crystallized in its modern form after two centuries of contentious infighting in a fractured scene of quackery, medical sectarianism, and pre–scientific revolution medical practice. While today we take for granted the social authority and esteem enjoyed by the physician, these were not always in evidence. For example, the father of J. Marion Sims, one of the pioneers of nineteenth-century surgery, reacted disapprovingly when informed of his son's chosen profession: "If I had known this, I certainly should not have sent you to college. . . . [Medicine] is a profession for which I have the utmost contempt. There is no science in it. There is no honor to be achieved in it."

Ultimately, the professional institution of "allopathic" medicine as we know it was able to secure a claim on legitimacy in three ways: through a commitment to evidence-based practice, a rigorous certification system that polices itself to maintain a body of competent practitioners, and a value orientation that prioritizes public health over personal economic gain. Training, self-regulation, and service orientation thus help define medicine as a profession.

Practical legitimacy, however, does not by itself convey a broader social authority. Physicians may be legitimate with regard to their professional practices, but they are unable to compel the public to heed their counsel on broader social issues. Authority is realized through the trust the public has placed in the medical profession for official duties such as treating diseases, healing ailments, prescribing medications, writing sick notes, and performing clearance physicals. Many of these roles are governed by legal regulations, but the professional authority of the physician is ultimately drawn from public trust.

The public's dependence on physicians can also be understood as a reliance on their expertise. Medicine's complexity and the gap in understanding between the laity and medical professionals were already evident by 1889, well before the era of modern medicine, when the U.S. Supreme Court, while justifying states' rights to provide medical certification, asserted that "comparatively few can judge of the qualifications of learning and skill which [a doctor] possesses" (*Dent v. West Virginia*, 1889). Patients trust that diagnoses and treatments decided upon by physicians represent an accurate, objective distillation of the current aggregated knowledge in the medical field—the conclusions that patients would themselves come to if they had received the same level of training as their physicians. The expertise of the doctor is a "shortcut to rationality (Starr, 1982), an informed extension of the patient's own decision-making capability into scientific and medical matters. For many people, regardless of their social standing or level of education, the medical professional is their principal liaison to the realm of the biological sciences. Physicians may be the only people with professional scientific training with whom many people will ever interact. It is from their responsible use of knowledge and expertise that physicians ultimately derive their authority to dispense professional opinions to individual patients and to society.

## PROFESSIONAL RESPONSIBILITY AND THE PUBLIC INTEREST

The American Medical Association (AMA), American medicine's oldest professional society, has set forth a code of ethics. Founded in 1847, the AMA was medicine's first successful attempt at creating a professional society in the United States, and it remains the country's preeminent medical body. The code of ethics is extensive and addresses the

particulars of many issues. It begins with a statement of principles, three of which are particularly relevant to the question of how physicians should engage with public policy.

Principle III imparts a responsibility to seek changes in laws that run counter to "the best interests of the patient" (in terms of health). Principle V calls for a commitment to education, including that of the patient. Principle VII requires a commitment to public health (American Medical Association, n.d.). Additional published opinions examining this code concern advocacy for change in law and policy, giving physicians the freedom to decide whether to participate in legally permissible activities they feel are warranted, as long as the motivation maintains the priority of the patients' best interests.

Medicine and public health have not always been unified; through much of the history of medical practice, medicine was seen exclusively as a service performed by a doctor for an individual patient. In the traditional narrative, physicians passively await patients—the clients—to seek them out before taking action on a particular problem. By assuming an active role in line with the service orientation of the profession, organized medicine has accepted the responsibility of guiding public policy in the name of public health. While this seems a significant addition to the mission of the physician, it is a logical extension of the role physicians play as guardians of and advocates for patients' health. The historical line separating public-health efforts from individual treatment through medicine was principally a consequence of our limited knowledge about the nature and spread of infectious diseases, but the widespread acceptance of germ theory in the nineteenth century played an important role in connecting the health of individuals with their place in society.

Rather than dealing strictly with pathologic issues and delivery of medical treatment, the physician's domain has expanded to include the mission of public health and relevant policy. Conceptually, this is a shift from focusing on the health of an individual patient to considering the health of a particular population as a whole. The practice of medicine should maintain the perspective of bringing broad benefits to society as a whole, rather than to a specific individual in the context of a specific medical case. Social issues that have public-health effects must be brought into the fold—meaning that medical practitioners should stay informed and receive training throughout their careers about public-health issues.

## SOCIAL MEDICINE: EXTENDING THE DOMAIN OF PUBLIC HEALTH

During the mid-nineteenth century, Karl Marx and other social theorists significantly influenced the medical establishment, bringing to the forefront the impact of social conditions on disease. The rise and success of germ theory and evidence-based medicine swept such ideas into the realm of politics and "social medicine," a field seemingly separate from clinical medicine. Epidemiology was the first area of medicine where the inherent interconnectedness of individuals' health was really appreciated. While there had been previous attempts to understand the spread of diseases in populations, the "father" of modern epidemiology is considered to be Dr. John Snow, who studied the spread of cholera in nineteenth-century London. Through a careful cataloguing of disease incidence in particular neighborhoods, he determined that contaminated water supplies (and specifically one contaminated water pump), rather than some amorphous airborne "miasma," were responsible for the spread of cholera (Vachon, 2005). Although his views encountered resistance from his contemporaries, his findings did help prompt the eventual development of modern urban plumbing and waste-disposal systems. Germ theory and the development of modern vaccines in the late nineteenth century served to underscore how critical it was to understand the spread of infectious diseases and appropriate means to control them not just on an individual level, but at the level of the population as a whole.

The impact of the group on the health of the individual goes beyond the direct transmission of pathogens. The actions and interactions of people within society can themselves drive the development of individual health risks and maladies. Dr. Jack Geiger, a great community-health pioneer of the 1960s, explained his work's significance thus: "The determinants of health lie in the social order, not in the medical process" (Rogers, 1970). Many of the maladies the medical field fights are rooted in social determinants; race, class, and gender have significant effects on medical outcomes. The doctor's aim is to improve health outcomes using evidence-based intervention; if evidence shows that social ills contribute to clinical maladies, how can those topics lie outside the realm of medicine? Consider the risk factors associated with release from prison. In the two weeks immediately following prisoners' release, their adjusted death rate is 12 times that of the general population. The greatest causes of death after release from prison are drug overdose, suicide, cardiovascular disease, and homicide (Binswanger et al., 2007). Factoring in the disproportionately high incarceration rate of African Americans (one in 13 between the ages of 30 and 34), the outcome of health disparity as a function of social disparity becomes clear. If an identifiable virus or environmental pollutant were responsible for a similar death rate, this would be considered a national epidemic necessitating urgent government action. But due to political and social realities in this country, some people reject the notion that prison policy can play the role of the proverbial "contaminated water pump," and will insist that prison policies remain outside the domain of medicine.

Where should the line be drawn? Racial laws, eugenics, and human experimentation were products of physician groups hoping to enact social change within the past century. Only in 2012 did the German medical community apologize for its role in the Holocaust (Sharav, 2012). Until 1973, *The Diagnostic and Statistical Manual of Mental Disorders* continued to list homosexuality as a medical illness; many psychiatrists actively promoted and practiced conversion therapy, now widely discouraged. In retrospect, these "medical" issues would obviously fall outside the accepted AMA ethics guidelines. What strongly held understandings

and beliefs of ours today will one day be looked at in shock? Do we take a risk in taking stances on "value-laden" topics? For example, homosexual behavior, while no longer misidentified as a mental illness, is still a significant risk factor in the acquisition of several diseases, including hepatitis and HIV. Would a physician concerned with public health be ethically correct in encouraging his or her homosexual patients to limit their exposure?

While overstepping is a risk of physician advocacy, the greater hazard lies in silence. In a 2008 address, the AMA apologized to the National Medical Association (the preeminent group of African American physicians in the United States) for the organization's long history of racism and exclusion of African Americans. During the fight for the passage of the Civil Rights Act of 1964, the AMA remained notably silent. Only in 1968 did it amend its constitution to exclude segregation (Washington, 2008). The issue of segregation may have seemed out of the profession's purview at the time, but upon reflection, this unfortunate omission on the part of America's most important professional medical society is a sign to physicians that they must be professionally active in combating laws and policies that promote inequality and injustice, whether or not explicitly health-related.

## BEING A MEDICAL ADVOCATE

If the primary goals motivating sex education in public schools are the prevention of sexually transmitted illness and adolescent pregnancy, then sex education clearly falls into the category of public health. Prevention of medically unwanted outcomes through education of the public is a widely accepted goal of public health. Presumably, sex education is such a preventive measure.

Much research has been done to examine the truth of that presumption. In 2009, SIECUS (the Sexuality Information and Education Council of the United States, a national organization devoted to the topic of sex education) reviewed federal, state, and private studies concerning the efficacy of federally funded abstinence-only programs. It found that these programs had been repeatedly determined to be ineffective, demonstrating a lack of improvement in almost any relevant outcome: sexual abstinence, number of sexual partners, rate of vaginal sex, condom use, teen pregnancy, and sexually transmitted disease (SIECUS, 2009). The only program that did validate abstinence-only intervention as effective used a curriculum inconsistent with that demanded by federal criteria; it included only medically accurate information without moralism or disparagement of contraception (Dreweke, 2010).

The question is not whether to advocate against the teaching of abstinence as a part of sex education per se, but instead to advocate against the way it is taught—federal sex education programs should not advise based on inaccurate medical information, nor should they be infused with moral judgment. Such programs have been repeatedly demonstrated to be ineffective. When an effective alternative exists, it is necessary to advocate for it.

Some physicians may be reluctant to engage with public-health questions because of the interconnectedness of health issues with more-provocative social and political issues. In advocacy, careful clarification of positions involves distinguishing clearly what portion of social policy genuinely affects public health. For example, when physicians consider the public-health impact of firearms, an important distinction must be made between the fight against gun ownership and that against gun violence (Mozaffarian, Hemenway, & Ludwig, 2013). Advocacy in sex education could similarly disentangle abstinence as an (arguably) moral virtue from abstinence as a separate birth-control method. The latter would allow for the teaching of abstinence alongside education about other forms of birth control. While an abstinence-only approach is more effective than complete silence on the topic, it must be carefully delivered with the exclusion of scientific falsehoods and social judgment.

A discussion of abstinence-only sex education should be one about the evidence and about the merits of the educational intervention. The merits of advocacy on behalf of that intervention should be clearly recognized. To fulfill their part in the dynamic relationship they have with patients, medical professionals must continue to advocate aggressively for them on all fronts. Engagement with norms that run counter to a physician's personal convictions is a common struggle. When physicians feel that a change in a "social" matter would benefit public health, they have a professional imperative to act, with assurance that they are within their professional rights to speak up about the matter on a public-policy level.

## AFTERWORD: PERSPECTIVES AND QUESTIONS FOR THE FUTURE

The increasing appreciation of the social determinants of disease necessitates the development of a physician's skill set beyond the direct practice of medicine with individual patients. We live in a world of increasingly interconnected communications. While this has the benefit of opening dialogue and discussion among people, the increased volume of beliefs and judgments threatens to diminish the relative impact of informed opinions. The saying "Everyone is entitled to his own opinion, but not to his own facts" (Daniel Patrick Moynihan) is particularly relevant to this idea. Zeal and volume are no substitute for a firm grasp of underlying facts and a consideration of the "big picture" into which they fit. Take the issue of vaccination, for example. Medical researchers and practitioners have extolled the revolutionary impact of vaccines for more than a century, and the successful eradication of scourges such as smallpox and polio have transformed the landscape of public health. This very insulation of modern people from the ravages of past epidemics, however, is part of what has contributed to the rise in the "anti-vaccination" community, whose members disparage the utility of many vaccinations and seek to implicate them as causes of all sorts of conditions, including autism, autoimmune diseases, and cancers. While no one can compel other people to vaccinate themselves or their children, physicians have a special responsibility to contest the deluge of misinformation about vaccinations. Staying silent and

hoping that poorly informed people are able to come to correct conclusions on their own is a breach of the public trust in physicians, who must be able to engage with laypersons in an open and convincing manner.

Related to the topic of vaccination is the issue of "herd immunity"—the concept of vaccinating or treating people not to safeguard their health, but to protect other people who may be at risk. For example, the recent use of Gardasil (Silgard) as a vaccine against HPV infection in women has proven very efficacious in eliminating the most significant cause of cervical cancer. Males can contract HPV and develop some medical complications, but they do not face a similar risk of cancer or serious disease. Is it ethical to recommend the vaccination of males, not for their own protection, but to prevent them from contracting HPV and infecting future sexual partners? A related issue involves HIV patients who still have relatively high CD4 T cell counts (that would not normally prompt antiretroviral treatment yet) but are given earlier-than-usual therapy to prevent transmission to others. These issues go beyond the traditional value of immunizations or treatments for an individual's own benefit to prophylactically treating an entire population. At what point does the risk of complications to an individual's health outweigh the benefits enjoyed by the treated population as a whole?

Vaccination is settled science, but what about questions of public policy for which there is no medical consensus? At what point does a physician cease to speak for the community, and instead speak of his or her personal opinions? Issues of human-tissue cloning, use of embryonic stem cells, and gene patenting are under debate in medical circles; at what point can the public expect a scientific consensus? A similar question concerns the "degrees of separation" between a particular topic and a potential health impact. Taken broadly, public-health issues can include a dizzying array of topics—adolescent obesity, illegal drug use, access to preventive health care, gun control, and the like. A physician may feel much more comfortable discussing the particulars of vaccination education than discussing a "sugar tax" to combat the spread of obesity, for example. The latter issue delves into areas of economics and political policy about which a physician may feel he or she has less expertise. There is no hard-and-fast rule for grey areas such as this; the best course of action is to make an honest assessment of one's own understanding of an issue, and make an effort to separate personal opinions from professional assessments. Taking such a position is often easier said than done, of course, but the recognition of a potential conflict and a genuine consideration of the nature of one's own positions is the best starting point toward a satisfactory resolution.

Public-health advocacy is an evolving capacity of physicians, and great care must be taken to address it in a responsible manner. The emphasis, however, should be on engagement and dialogue, rather than on sheltering within the known confines of individual patient care. Physicians may not always have the right answer to every health issue (and they should have the humility to recognize this), but they necessarily play a fundamental and decisive role in informing a public debate along scientific, empirical, and ethical lines.

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# Intersex Management in the United States and Non-Western Cultures

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In Western nations, there is growing agreement about ethical approaches to clinical intersex management. At the same time, as Western-trained physicians increasingly encounter intersex patients in other parts of the world, new ethical tensions arise. Which cultural values are fair parameters for gender-assignment decision-making, particularly in cultural milieus where there is social and economic inequality between the sexes? How can physicians uphold universal bioethical principles while remaining culturally sensitive? Physicians have a primary commitment to patient beneficence and universal human rights, requiring physicians to promote concordance between the child's assigned gender and his or her likely future gender identity. Ultimately, the potential patient distress posed by gender dysphoria fundamentally outweighs the influence of local cultural factors such as economics, gender politics, and homophobia.

## INTRODUCTION

We live in a sexually dimorphic reality, where one is required to choose either male or female when filling out everything from census questionnaires to voter registration forms. Likewise, medical records neatly report sex as male or female. Yet significantly many babies are born each year with ambiguous genitalia, an unclear sex assignment, or both, leading some to argue that gender is truly a continuum, not a binary. According to the Intersex Society of North America, 1 percent of babies physically differ from "standard male or female" (ISNA, "How Common Is Intersex?"), while 0.1 to 0.2 percent of babies require medical intervention and surgery to "normalize" their genital appearance (ISNA, "How Common Is Intersex?").

Such genital ambiguity can be caused by a variety of disorders of sex development, including congenital adrenal hyperplasia (CAH), androgen insensitivity syndrome, and 5-alpha-reductase deficiency. Congenital adrenal hyperplasia is characterized by increased production of androgens, resulting in the genital virilization of chromosomal females. Meanwhile, genotypic males with androgen insensitivity syndrome have cells that cannot respond to androgens, hindering the development of normal male genitalia and the later expression of male secondary sex characteristics during puberty. And in 5-alpha-reductase deficiency, genotypic males have difficulty converting testosterone to dihydrotestoerone (DHT). Because DHT is a more potent androgen than testosterone, this deficiency means that affected neonates are often born with ambiguous or feminized genitalia. However, at puberty increased testosterone levels may lead to sufficient generation of DHT to promote subsequent masculinization (PubMed Health, "Intersex").

For many of these intersex patients, complex decisions must be made to determine the appropriate gender of rearing and whether to pursue "corrective" genital surgery. Such decision-making raises ethical issues, including the roles of the various actors involved (physicians, parents, and patients), as well as which parameters are appropriate to take into account during this process. Other ethical concerns include the patient's right to bodily integrity, informed consent, and disclosure of his or her intersex status.

In the United States and other Western nations, clinical management of intersex infants has evolved significantly over the past half century. Harsh critiques by adult intersex activists and an enhanced scientific understanding of gender-identity formation have contributed to a greater appreciation of the ethical issues involved in gender assignment. At the same time, as Western-trained physicians increasingly encounter intersex patients in other parts of the world, new ethical tensions arise. Which cultural values are fair parameters for gender-assignment decision-making, particularly in cultural milieus where there is social and economic inequality between the sexes? And how can physicians uphold universal bioethical principles while remaining culturally sensitive in such settings?

## INTERSEX MANAGEMENT IN THE UNITED STATES

According to historian Alice Dreger, for most of modern Western history intersex people were integrated into the general population, adopting either a male or a female identity in accordance with binary gender norms. They maintained their ambiguous genitalia without significant psychological harm or social stigma. However, by the late 1800s the mounting anxiety over homosexuality—"abnormal" sexual behavior—led physicians to pay increasing attention to "abnormal"genitalia and perform corrective surgeries; these included surgeries for enlarged clitorises and hypospadias (in which the urinary hole is in an abnormal location in males) (Dreger & Herndon, 2009).

Still, corrective surgeries did not become the medical norm until the 1950s, when Johns Hopkins psychologist John Money and colleagues developed the "optimum gender of rearing" model. This model posited that children were

born gender neutral and that gender identity was a result of upbringing rather than genetics or hormone exposure; thus, intersex children with an assigned sex and corrective surgery to match this assignment (before age 2) would successfully adopt this gender identity. Physicians largely determined the child's "true" sex with limited input or informed consent from parents; further, often the patient was never informed of having been born intersex, in order to limit possible psychological distress (Dreger & Herndon, 2009).

For several decades beginning in the 1950s, clinicians were biased toward female gender assignment, as it was easier to fashion a vagina than a "reasonably sized" penis. In other words, a primary value was placed on genital aesthetics and the ability functionally to penetrate or be penetrated (Dreger & Herndon, 2009). For a penis to count as functional, surgeons expected it to have the ability to become erect appropriately and be a conduit for urination and ejaculation. In contrast, surgeons at that time believed that a vagina merely needed to be a hole large enough to fit a penis, as it was not expected to be self-lubricating or sensitive to sexual stimulation. As a result, a large number of intersex infants were assigned female (Dreger, 1998), as "it's easier to make a hole than build a pole" (Gorman & Cole, 2004).

This bias toward female assignment is evidenced by the famous John/Joan case—Money's prototypical success story for the "optimum gender of rearing" model. Baby John, one of two identical twin boys, had his penis damaged during a botched circumcision, so Money and colleagues decided to transform John surgically into Joan. Joan was raised as a girl, and Money reported in the medical literature that the sex reassignment had been successful (Fausto-Sterling, 2000a). For example, in 1975 Money wrote that no one would ever suspect that Joan was born a boy: "Her boyish behavior is so normally that of an active little girl, and so clearly different by contrast from the boyish ways of her twin brother, that it offers nothing to stimulate one's conjectures" (Kipnis & Diamond, 1998). Money's work seemingly provided scientific evidence of the malleability of gender identity at a young age.

However, in the mid-1990s sexologist Milton Diamond followed up with Joan, and he discovered that Joan had in fact consistently identified as male since her youth. Joan preferred boys' toys, activities, and clothing, and at age 14 she decided to transition formally back to the male gender (Diamond & Sigmundson, 1997). The publication of Diamond's findings discredited the claimed success of Money's gender-reassignment protocol, in the process debunking the theory of gender neutrality and pliability at birth.

Around this time, adult intersex patients who had been subjected to sex-reassignment surgery as children began publicly to criticize the clinical management of their condition. This coincided with the burgeoning of the intersex activist movement, spurred by Cheryl Chase's 1993 founding of the Intersex Society of North America (ISNA) (Chase, 1998).

In her 1998 article "Hermaphrodites with Attitude," Chase recounts that as a teenager she realized she had no clitoris and was incapable of reaching orgasm, but she never understood why. After obtaining her medical records, Chase learned in her twenties that she was a "true hermaphrodite" (Chase, 1998) and had been raised as a boy for a year, until a clitorectomy was performed and she was reassigned as female. Along the way, Chase's doctors not only had failed to disclose her medical history to her, but had actively obstructed her efforts to obtain her own medical records. Chase relates her emotional turmoil upon discovering her intersex past: "To myself, I was a freak, incapable of loving or being loved, filled with shame about my status as a hermaphrodite and about my sexual dysfunction" (Chase, 1998).

As a result of the experiences of Chase and her allied intersex activists, the ISNA currently advocates complete disclosure to intersex patients, as well as gender assignment at birth *without* surgery. The ISNA explains, "Genital 'normalizing' surgery does not create or cement a gender identity; it just takes tissue away that the patient may want later" (ISNA, "What Does ISNA Recommend?"). The ISNA asserts that such surgery on young children causes irreversible damage and denies them agency regarding their own bodies. Instead, the ISNA believes that corrective surgery is permissible only once the child is old enough to decide with fully informed consent (ISNA, "What Does ISNA Recommend?").

Other writers maintain that intersex individuals should be able to legally proclaim a third, hermaphroditic, nonfemale/nonmale gender identity. On passports Australia permits individuals to label themselves "X," which stands for unspecified sex or intersex. And the Australian state of Victoria issues birth certificates with the sex listed as indeterminate/intersex (Meyer-Bahlburg et al., 2004).

While the ISNA claims to speak on behalf of the general intersex community, in reality intersex adults express a variety of opinions about appropriate clinical management policies. For example, in a 2004 study surveying 72 adult intersex patients in the eastern United States, 15 percent believed that a third gender category should be available to children with ambiguous genitalia. And 33 percent of those surveyed agreed that intersex children should not undergo corrective surgery before they are able to give fully informed consent. In contrast, 47 percent of respondents stated that in hindsight, they felt that their corrective genital surgery should have occurred during infancy. There is little agreement within the adult intersex community about the appropriate timing of surgery; this lack of consensus underscores the ethical uncertainty inherent in the medical management of intersex infants (Meyer-Bahlburg et al., 2004).

One of the most fraught ethical concerns centers on the rights of parents versus intersex children to make clinical decisions about genital corrective surgery. Because young children generally lack decision-making capacity, U.S. law recognizes the parental right to make medical decisions on their behalf. This parental agency assumes that parents

know their children best and will act in their best interests. However, in the case of intersex children, parents may not always be the best arbiters. For example, the existence of congenital birth defects (such as ambiguous genitalia) may hamper early parent-child bonding, and societal stigma and emotional distress may bias parents toward early corrective genital surgery (Lloyd, 2005).

Such parental medical decision-making rights are not absolute, and under the doctrine of *parens patriae* courts can intervene to prevent death or serious harm to the child. For example, most states restrict parents from sterilizing their children, as a person's right to make decisions concerning reproduction is constitutionally protected. Similarly, per 1996 Congressional legislation, parents are prohibited from consenting to female genital cutting of their daughters as part of cultural rituals. This law was passed under the auspices of protecting a child's right to bodily integrity. By extension, some argue that corrective gender-reassignment surgery in intersex children is likewise a violation of their bodily integrity and reproductive rights, particularly because the surgery may impair reproductive ability or sexual sensitivity (Lloyd, 2005). Historian Alice Dreger explains:

While it is easy to condemn the African practice of female genital mutilation as a barbaric custom that violates human rights, we should recognize that in the United States medicine's prevailing response to intersexuality is largely about genetic conformity and the "proper" roles of the sexes. Just as we find it necessary to protect the rights and well-being of African girls, we must now consider the hard questions of the rights and well-being of children born intersexed in the United States. (Dreger, 1998)

As a result, some camps have called for a complete moratorium on normalizing genital surgery in intersex children. Others maintain that enhanced parental informed consent is adequate; in other words, as long as physicians fully explain what "intersex" means, as well as various aspects of the surgery (alternatives, ethical issues, risks, and whether it's medically necessary), parents should make the ultimate call. And others have criticized such "all-or-nothing" approaches (Muckle, 2006). Instead, they call for the involvement of hospital ethics committees and consultants in bringing together physicians and parents to determine the best interests of the child, on a case-by-case basis (Muckle, 2006). While this approach represents a pragmatic middle road, the availability and utility of ethics consultants or committees, particularly ones with expertise in intersex issues, vary considerably among hospitals.

In addition to the charged issue of who should have decision-making agency, there is considerable ethical debate concerning the parameters and values within which it is ethically permissible to make such decisions. For example, should concerns such as potential societal stigma, shame, or bullying come into play? If keeping a child's genitalia ambiguous would impair child-parent bonding, is this an acceptable reason to pursue surgery? Or do parents have an ethical obligation to overcome their prejudice and care for their child? What is the relative value of genital aesthetics, reproductive ability, phallic size (in men), ability to be penetrated (in women), and intact erotic sensation? And what are the potential risks that physicians and parents will choose the wrong gender assignment, given the limited scientific knowledge concerning gender-identity formation? Is surgery more acceptable for intersex conditions in which a majority of patients end up identifying as a common gender?

To grapple with the complexities of intersex clinical management, the Lawson Wilkins Pediatric Endocrine Society in the United States and the European Society for Pediatric Endocrinology organized the International Consensus Conference on Intersex. This conference included more than fifty international experts on intersex management and compiled their responses into a consensus statement, published in 2006 in *Pediatrics*, the official journal of the American Academy of Pediatrics (Lee, Houk, Ahmed, & Hughes, 2006).

The consensus statement strongly supports gender assignment as male or female, after a detailed examination of the baby by a multidisciplinary team of physicians. It emphasizes the importance of mental-health support from psychologists and psychiatrists, as well as the utility of support groups and medical ethicists. It also endorses complete medical disclosure to both parents and patients. And while the document supports parental decision-making rights, it maintains that patients should have input once they are "sufficiently developed for a psychological assessment of gender identity" (Lee et al., 2006). Accordingly, if a child experiences gender dysphoria and insists upon a gender transition, this desire should be respected. The goal of clinical management is not only gender assignment and normalized genital appearance, but also ensuring patient quality of life—which encompasses the ability to form intimate relationships, and sexual functioning and sensation. It follows, then, that clitoromegaly should result in surgical intervention only in cases of severe virilization; in such instances, surgery should prioritize preserving erectile ability and innervation of the clitoris, rather than strictly cosmetic normalization.

In contrast, in the United States, precedence was historically given to cosmetic correction, to limit stigma and teasing and facilitate improved parent-child bonding. The *Pediatrics* consensus statement debunks the scientific validity of this alleged enhanced bonding, and it charges medical staff to minimize shame and stigma, for example by taking photographs when patients are under anesthesia for a procedure (Lee et al., 2006).

For certain well-studied intersex conditions, the statement makes clear recommendations regarding the optimal gender of rearing. For example, it advises that markedly virilized 46,XX infants with CAH be reared as female, while an infant with a micropenis should be reared as male. It also notes that 100 percent of 46,XY complete androgen insensitivity syndrome babies assigned female in infancy maintain a female identity; for these patients, it recommends removal

of the testes to prevent malignancy (though this removal can be delayed until adolescence, as malignancy normally does not develop until at least age 14) (Lee et al., 2006).

While many of these recommendations are currently followed, in the clinical setting preserving female fertility is often given higher priority than preserving male fertility. Academics hypothesize that "this difference might be because physicians and parents believe that motherhood is more important to females than fatherhood is to males" (Diamond & Beh, 2008). It is ethically troubling that important clinical decisions are being made based on deep-seated societal gender-role assumptions. And while early disclosure to both parents and patients is now the norm, insufficient psychological counseling and support are still major problems (Diamond & Beh, 2008). This raises the question: is it truly beneficent for physicians to impart potentially psychologically damaging information without giving pediatric patients the tools to process it? The medical establishment has an ethical obligation both to practice disclosure and to help ameliorate any psychological trauma engendered by such disclosure.

**INTERSEX MANAGEMENT IN NON-WESTERN CULTURES**

Although there is growing agreement in the United States regarding the ethical values important in intersex management, it is less clear whether these principles are applicable in non-Western settings. Are "Western" bioethical values indeed fundamentally universal and thus viable in other cultural milieus, where social, political, and economic inequity between the sexes may influence clinical decision-making? How can physicians remain culturally sensitive without abandoning their commitment to informed consent, personal autonomy, bodily integrity, disclosure of medical information, and beneficence? And is it just to take into account extreme societal stigma/shame (including the potential for violence) during the sex-assignment decision-making process?

Physicians treating ethnic Indians living in Malaysia have observed the overriding influence of economic concerns in intersex management. Physician Ursula Kuhnle and colleagues noted that for Indians living in Malaysia, daughters present a major financial burden for the family, as they must pay a dowry; in contrast, sons increase the family's wealth. For this reason, many Indian families "took off with their ambiguously born child" (Kuhnle & Krahl, 2002) after physicians suggested female sex assignment. Kuhnle and collaborators contrasted this with the behavior of Muslim Malay families, who usually did not object to female sex assignment—presumably due to the increased economic power and independence of Muslim Malay females (Kuhnle & Krahl, 2002).

Similarly, physicians working in India have reported that economic factors profoundly affect intersex clinical management. If a woman is unmarried or divorced, she may be unemployable and reduced to "wretched poverty because of the stigma attached to being single" (Warne & Bhatia, 2006). In other words, she will remain economically dependent on her parents forever. In contrast, single men are able to find jobs and live independently. If an intersex child is raised as an infertile female who does not menstruate, she will not be able to find a husband; even if the family tries to hide her infertility, once the husband discovers the truth this provides grounds for immediate annulment (Warne & Bhatia, 2006).

A pediatric endocrinologist in northern India related how parents of intersex children consistently valued female fertility over sexual function. "These social considerations were ubiquitous, no matter what the religion of the patient" (Warne & Bhatia, 2006). During discussions with the doctor, the parents would typically offer arguments along the lines of: "Doctor, we will have to raise the baby in our society, not yours." This physician reported that as a result, in India, parents rather than physicians assumed the main decision-making role during sex assignment (Warne & Bhatia, 2006).

Parents of intersex children in India often fear that their children will be kidnapped by the *hijras* if their intersex status becomes public. The hijras are males who adopt a female gender identity by having part or all of their genitals removed, in addition to dressing as female (Nanda, 1985). They live in groups apart from mainstream society and are generally stigmatized and viewed suspiciously. The hijras traditionally make a living by singing and dancing at public celebrations such as weddings, and they also often engage in prostitution with male customers (Warne & Bhatia, 2006). The public predominantly believes that hijras kidnap intersex infants to "claim" them, yet there is scant evidence to support this superstition. Still, on occasion the popular press prints allegations about hijras kidnapping young boys for sex or prostitution (Nanda, 1985).

Parents may worry that their intersex children will suffer societal discrimination if their condition becomes well known. Indian physicians explain that "this kind of discrimination is real . . . and occurs in village communities as well as in sophisticated city environments" (Warne & Raza, 2008). It is important to consider how such extreme parental fear may influence decision-making, especially with respect to the timing of corrective genital surgery that erases any outward sign of sexual abnormality.

Similarly, a 2012 report from Cairo, Egypt, found that economic motives drive a large percentage of families to choose the male gender. Specifically, 60.35 percent of intersex patients are reared as male, because "in Egyptian society, female infertility precludes marriage, which also affects employment prospects" (Shawky & Nour El-Din, 2012). And a 2011 study of intersex children in Port Harcourt, Nigeria, found that the societal importance of males makes it "difficult for parents to accept the fact that there [*sic*] male babies could be females" (Jaja, Yarhere, & Anochie, 2011). Instead of pursuing clinical intervention, many parents whisk away their children under the pretense that the problem is spiritual rather than medical (Jaja et al., 2011).

In Saudi Arabia the clinical management of intersex infants

is likewise influenced by the economic, social, and political benefits of being male. A strict segregation between the sexes is enforced, and women have limited visibility in public life. Women are not allowed to drive and must obtain the permission of a male sponsor to travel or engage in commerce. In public, they are required to cover themselves in floor-length cloaks and headscarves. Women are prohibited from appearing in court and are relegated to separate stores, restaurants, and offices within companies (Zoepf, 2010). And women gained the right to vote only as recently as September 2011, in part due to the pressure from Arab Spring uprisings (MacFarquhar, 2011).

A 1994 study attributed male gender preference in Saudi intersex management to such economic, social, and cultural factors. An intersex individual reared as an infertile female will be unable to find a husband, causing several social repercussions:

A woman who is not well-educated remains unemployed but in general males are always employed. An unmarried woman lives with her parents. . . . After a certain age, an unmarried woman loses considerable social status. . . . In this community where unmarried males and females are segregated, it is preferable to be an infertile male with an inadequate penis than to be an infertile female with primary amenorrhea and requiring estrogen substitution. (Taha, 1994)

A 20-year retrospective study by Dr. Nasir Al-Jurayyan in a pediatric endocrine clinic in Riyadh, Saudi Arabia, found a high incidence of congenital adrenal hyperplasia in genetic females (46,XX) with ambiguous genitalia, owing to high levels of consanguinity. Out of the 25 XX congenital adrenal hyperplasia patients originally assigned male due to extreme virilization, four (16 percent) refused reassignment to the female gender. In contrast, all of the 46,XY patients reared female accepted physician recommendations to be reassigned as male (Al-Jurayyan, 2010).

Dr. Al-Jurayyan's report relates that once the genital ambiguity is discovered, the clinical team discusses both medical details and the Islamic guidelines for sex reassignment (as promulgated by Saudi Wahhabi religious leaders) with the patient's family. The Wahhabi Islamic guidelines state:

Those who have both male and female organs need to be investigated and if the evidence is more into a male, it is then permissible to treat him medically (by hormones or surgery), to eliminate his ambiguity, and raise him male. If the evidence is more into a female, it is permissible to treat her medically (by hormones or surgery) to eliminate her ambiguity, and raise her as a female. (Al-Jurayyan, 2010)

In contrast, a sex-change operation performed on a "completely developed gender to the opposite sex" is always prohibited. Dr. Al-Jurayyan also conveys the tension between such Islamic religious guidelines and the reality of the "dominating role of male gender in the community," which predisposes families toward male gender assignment. Al-Jurayyan asserts that such cultural concerns "should not overrule the Islamic Laws which should not be ignored and given a prime consideration" (Al-Jurayyan, 2010).

This preference for males is exemplified by a 1998 paper detailing the psychological aspects of Saudi intersex patients initially reared female; physicians noted the powerful familial pressure to reassign them as male. In one case, though the patient strongly identified as female, when physicians recommended against male reassignment the family members became so upset that they insisted upon prompt discharge from the hospital (Elsayed, Al-Maghraby, Hafeiz, & Tasha, 1998).

This societal male dominance also strongly affects the ease of adjustment to a different gender. Dr. Yasser Jamal, a Saudi surgeon who has performed more than 200 operations on intersex patients, explains that patients normally experience a smooth transition from female to male. In contrast, men often find it difficult to be reassigned as female, as "the restrictions of being female in Saudi Arabia [are] difficult to cope with" (Usher, 2004).

This complex situation for intersex individuals in a society where rights are tied to gender hearkens back to the 1843 case of intersex Connecticut resident Levi Suydam. Suydam wanted to vote as a Whig in a close local election; however, only men held the right to vote. As a result, a physician was brought in to determine Suydam's gender. Upon seeing Suydam's phallus and testicles, the physician declared him a male entitled to the franchise—and the Whigs won the election by one vote. But a few days later the doctor discovered that Suydam menstruated regularly, though it's unclear whether at that point he lost his right to vote (Fausto-Sterling, 2000b). This American example sheds light on how cultural context can make gender identity and assignment politically loaded, particularly when rights are tied to sexual anatomy, as they are in Saudi Arabia.

Furthermore, while patient disclosure is a widely accepted norm in American intersex clinical management, some have argued that it may not be optimal in an environment where the family patriarch traditionally holds sole decision-making authority. For example, in 2003 the *Hastings Center Report* published a case study about a 13-year-old intersex boy from an unnamed Middle Eastern country. Though he was originally brought to the hospital for hypospadias, bleeding through the penis, and abnormal breast development, it was soon discovered that the boy was genetically XX and had a uterus and ovaries. He was diagnosed with congenital adrenal hyperplasia and required hysterectomy and oophorectomy (removal of the ovaries) in order to prevent bleeding through the penis (representing menstruation) (Diamond, Systma, Dreger, & Wison, 2003).

The parents requested that all of the surgeries (for hypospadias, bilateral mastectomy, hysterectomy, oophorectomy, and nephrectomy for a nonfunctioning kidney) be performed at the same time without telling the child of his intersex condition or his female reproductive ability; in other

words, they wanted the patient to be completely left out of the decision-making process. Still, it is clear that the boy did support the mastectomy to "avoid teasing." The case study also explains that the culture favors males, the parents would have a difficult time accepting their child as a female, and that the child might be at risk for physical harm or murder if he became homosexual. This case presents an ethical dilemma; the surgeon did not feel comfortable operating without the child's consent, while the family maintained that the father should make this important decision without disclosure to the patient (Diamond et al., 2003).

The ethically contentious nature of this issue is highlighted by the three commentaries published in the *Hastings Center Report* alongside the original case. In his response, pediatric urologist David Diamond delineates the fundamental tension between the patient's autonomy and the needs of his family. Diamond notes that a "family-centered model" supports the father's right to make a decision, as it gives the smooth functioning of the family unit the biggest priority (versus the independence of its individual members). For instance, if the child's reassignment to female would make it impossible for the family to return home due to societal prejudice, this reality should be a factor in decision-making (Diamond et al., 2003).

Meanwhile, ethicist Alice Dreger and pediatric endocrinologist Bruce Wilson vehemently attack the case study's proposed nondisclosure to the intersex boy. They assert that intersex children have a right to be informed and make important decisions about their bodies, regardless of culture. In other words, children's genitals are not "an acceptable locale for cultural relativism" (Diamond et al., 2003).

Dreger and Wilson also make an appeal to the pragmatic, explaining that disclosure is necessary given the ongoing nature of intersex clinical management, particularly endocrine management; such disclosure facilitates greater patient cooperation. Moreover, the authors note that this case presents a false sense of urgency about the need to fix the problem. In reality, halting puberty (and its attendant menstruation and breast development) through once-monthly leuprolide injections represents a reasonable way to delay decision-making until the child is mature enough to participate (Diamond et al., 2003). Still, this tactic might face cultural obstacles, such as limited access to hormones and public shame if it were discovered the child still had internal female anatomy.

It is due to this societal prejudice that ethicist Sharon Sytsma maintains that the physicians should accede to the parental request for surgery without disclosure. Sytsma writes that "not performing the surgery means the child will continue to be taunted and suffer almost certain disenfranchisement and rejection, and that he quite possibly will be murdered" (Diamond et al., 2003). However, Sytsma is conflating gender identity and sexual orientation; while the case report indicates that homosexuality is punishable by death, it is less clear if being intersex poses an equal risk of death.

Sytsma also contends that "changing the boy is certainly more within our power than changing his culture, and the surgeries will make it easier for him to thrive in that culture" (Diamond et al., 2003). This assertion presents an ethically slippery slope. In a race-conscious society where being white provides socioeconomic advantages, should we allow parents to have their young children's skin bleached or Asian eyelids Anglicized? How is it ethical to surgically modify children's bodies without their consent, on the basis of societal prejudice?

Sytsma goes further by recommending that the child remain male in order to ensure his heterosexuality in a homophobic culture. She draws on research indicating that XX individuals reared male with pre/perinatal and postnatal/pubertal elevated androgens are usually gynephilic. She also asserts that if surgery is not performed the "female hormones may incline him to be attracted to males" (Sytsma, 2006). According to Sytsma, then, the child should remain male because he is likely attracted to females; in addition, surgery should be undertaken to ensure that he does not develop an attraction to males (Sytsma, 2006). Sytsma's contention is troubling in that it endorses gender assignment and genital surgery to reinforce societal norms concerning sexual orientation. And by performing this surgery, physicians are condoning the homophobia that spurred it in the first place. At what point does the medical establishment become a tool to blunt diversity of sexual orientation and undermine human rights?

In Iran homosexuality is a crime punishable by lashing or death; two gay teenagers were executed in 2005 in the Iranian city of Mashad (Fathi, 2007). To try to eliminate homosexuality from the country, Iran encourages homosexuals to undergo sex-change operations by heavily subsidizing them (Tait, 2007). Is it ethical for physicians to follow in Iran's footsteps and use surgery to curb homosexuality? At what point does medical intervention stop prioritizing the patient's best interests and become an agent of social engineering? And what is the distinction between "normalizing" genital appearance and "normalizing" sexual orientation to heterosexuality? Are they fundamentally ethically dissimilar, or is the latter more scandalous to Westerners because homosexuality is increasingly embraced in Western society?

## DISCUSSION

While the clinical management of intersex infants remains fraught with contentious ethical issues, in the United States there is growing agreement about ethical approaches to gender reassignment. The 2006 consensus statement in *Pediatrics* enumerates the important issues to take into account (such as patient quality of life, sexual functioning, and sensation), and it makes specific recommendations regarding the optimal sex of rearing for various intersex conditions; these guidelines are based largely on the predicted gender identity of the patient and the potential for future fertility. Moreover, the statement emphasizes that children who later experience persistent gender dysphoria should undergo psychological evaluation and be supported in transitioning to the desired gender (Lee et al., 2006). In

other words, the primary value is placed on a concordance between the child's gender assignment and internal gender identity—an important component of quality of life.

However, the 2006 consensus statement fails to take a stance on the myriad ethical issues that arise in the non-Western world, such as the appropriateness of taking into account the stark economic and political inequality between the sexes. In an increasingly globalized world, where Western physicians frequently work abroad and treat culturally diverse immigrants, such lack of globally conscious guidance is troubling. While some may argue that the field of bioethics itself is fundamentally "Western" (Ryan, 2004) and lacks "adequacy and credibility" (Ryan, 2004) abroad, the reality is that "Western" bioethical principles have been adopted globally through the work of the International Bioethics Committee (IBC) of the United Nations Educational, Scientific, and Cultural Organization (UNESCO). UNESCO's 2005 Universal Declaration of Bioethics and Human Rights, drafted by the IBC (UNESCO, "UNESCO's General Conference Adopts"), emphasizes maximizing benefit and minimizing harm (beneficence and nonmaleficence), patient autonomy, and informed consent (UNESCO, 2005). In this context of increasing interaction with the non-Western world, the 2006 consensus statement must be expanded to incorporate globally relevant concerns.

**Gender Assignment and Corrective Surgery**

In an ideal world, infants with ambiguous genitalia and uncertain gender assignment would grow up in a third gender category, with the ability to decide later on a gender for themselves. However, in our imperfect world both rampant societal stigma and other pragmatic realities preclude such a path—necessitating timely gender assignment. Such gender assignment should be guided by comprehensive medical analysis and seek to conform to the child's likely future gender identity. For example, more than 90 percent of XX infants with CAH and all XY patients with complete androgen insensitivity syndrome who are assigned female in infancy continue to identify as female (Lee et al., 2006). Still, gender assignment should not necessarily include genital corrective surgery. Instead, physicians should discuss with parents the benefits of delaying surgery until the child is old enough to be a part of the decision-making process, particularly in cases where surgery may impair erotic sensation or fertility. Such a postponement helps preserve the child's fundamental right to bodily integrity.

However, in some cases corrective surgery in infancy may be in the child's best interest. For XX CAH patients with extreme external virilization (for example, typical male-appearing genitalia as opposed to mild clitoromegaly), it may be medically beneficial to undertake corrective surgery sooner rather than later. In this context, early surgery to feminize the genitalia and separate the vagina from the urethra may prevent medical complications as well as minimize psychological distress and gender dysphoria. Nevertheless, in these cases surgeons should be careful to preserve fertility and sexual sensation.

**Disclosure and Informed Consent**

The 2003 *Hastings Center Report* case study broached the issue of disclosure and informed consent in a global setting. In this case, parents requested that a 13-year-old intersex boy undergo surgery to remove his internal female genitalia without informing him of his intersex condition. Thus, the clinical team faced two separate questions with ethical implications: should the child undergo surgery to align him with the male gender, and should the child be informed about his female genotype? (Diamond et al., 2003).

With respect to the latter question, it is imperative that physicians be open and honest with the patient. Dishonesty would only confuse the boy, destroy the integrity of the patient-physician relationship, and impede patient compliance; a patient who understands the importance of his medication regimen is more likely to follow through with it. While the child may be traumatized upon discovering his intersex condition, such distress can be limited by appropriate psychological and familial support. Patient disclosure is essential to ensure that paternalism does not go too far. Parents and physicians are empowered to act on the patient's behalf as long as the patient lacks decision-making capacity; however, as the patient grows older, he should be made aware of his medical history so that he can partake in his own medical decision-making.

Turning to the ethical question of whether parents can consent to surgery for their child, Diamond's *Hastings Center Report* case commentary argues that the family-centered model supports the father's right to make a decision; this model gives top priority to the well-being of the family unit as a whole (Diamond et al., 2003). However, this approach ignores that the physician's most important obligation is to the child. The child, not the parents, will be most intimately affected by any decisions that involve his gender assignment, genital appearance, fertility, and sexual sensation. This primary emphasis on the child's well-being is especially important in cases where the child is too young to speak in his own behalf; in such instances, enhanced parental education and informed consent, as well as the involvement of hospital ethics committees, are optimal to ensure that the parents are reaching decisions in line with the child's best interests.

**Globally Specific Parameters: Economics, Politics, and Homophobia**

In many of the cases described, economic and political reasons were the chief motivators for intersex patients to maintain or adopt a male gender identity, even if it went against medical recommendations. However, physicians have a fundamental obligation to promote both human welfare and human rights, and they should not condone medical decision-making that legitimates societal prejudice or inequality between the sexes. Physicians have a primary obligation to ensure patient well-being as reflected by concordance between a patient's gender assignment and internal gender identity. Allowing cultural factors such as economics, politics, and homophobia to supersede this concordance unethically puts the child at risk for gender dysphoria. Gender dyspho-

ria often results in extreme distress and is associated with emotional and behavioral problems (Meyer et al., 2002).

Moreover, permitting the consideration of economics, politics, and homophobia would create a problematic slippery slope. For example, could a U.S. couple demand male gender assignment on the basis of the nation's gender pay gap—claiming that their child would be economically disadvantaged as a female? (Rampell, 2011). Similarly, could a U.S. couple demand male gender assignment based on the persistent underrepresentation of women in U.S. politics? (Lawless and Fox, 2012). And if intersex clinical decision-making taking into account extreme homophobia is permissible in Iran, what if a U.S. couple demands a heterosexual child, based on extensive bullying of gay teenagers (and resulting gay suicides) in the United States? (McKinley, 2010). What if U.S. parents argue that being heterosexual is in the patient's best interest, as otherwise he will be unable to marry in the states that prohibit gay marriage? Permitting economics, politics, and societal homophobia to shape clinical decision-making creates a dangerous precedent, and it turns the well-meaning physician into an agent enforcing perceived social norms.

Finally, making important medical decisions based on cultural factors is dangerously short-sighted. Cultures are fluid and societal conditions are constantly in flux, making the future largely unpredictable.

For example, though economic obstacles exist for women in India and Saudi Arabia, these countries are currently experiencing an increasing number of women in the workforce. The *Times of India* reports that "women in the IT workforce grew from 4.21 lakh in 2006 to 6.7 lakh in 2008" (one lakh equals 100,000) ("Caution: Women at work," 2011). And in Saudi Arabia, the government is now encouraging women to find work; this is in part motivated by its desire to decrease unemployment benefit payments. The Saudi government has been working with Glowork.net, a new work-recruiting site for women. The government has also been pushing through a program to feminize the workforce in certain settings, such as female lingerie stores (Hamdan, 2012). Saudi women have had trouble finding work in the past due to the strict segregation of the sexes, meaning that female workers must work in offices separate from their male colleagues; the cost of maintaining two offices thus provides disincentives for companies to hire women (Hamdan, 2012). To surmount this obstacle, Saudi Arabia is currently planning a new city exclusively for female workers, which is predicted to generate 5,000 jobs in the textile, pharmaceutical, and food-processing industries (Baker, 2012). In addition, the advent of the Internet and cloud-computing technology has allowed Saudi women increasingly to work for companies from home. This allows companies to maintain the strict separation of the sexes without having to take on the economic burden of two offices (Hamdan, 2012).

While women in Saudi Arabia continue to be deprived of many political rights, conditions are far from static. For example, in 2011 Saudi women gained the right to vote and run in municipal elections (MacFarquhar, 2011), and Saudi women were permitted to compete in the Olympics for the first time at the 2012 London Summer Olympics. There, 16-year-old Wojdan Shaherkani, an athlete in judo, made history as the first female Saudi Olympic competitor (Addley, 2012). And while Saudi women still lack the right to drive, King Abdullah told foreign reporters that Saudi women will likely drive at some point in the future. In the meantime, Saudi activists continue to press for change. In October 2013 a few dozen Saudi women with driver's licenses from other countries got behind the wheel in protest. "We are looking for a normal way of life, for me to get into my car and do something as small as get myself a cappuccino or something as grand as taking my child to the emergency room," explained Saudi activist Madiha al-Ajroush (Hubbard, 2013).

The 2003 *Hastings Center Report* case probed the idea of using future sexual orientation as a clinical decision-making parameter in societies with extreme homophobia. Specifically, ethicist Sharon Sytsma advocated for solidifying the child's male gender identity through surgery, to ensure his heterosexuality in a homophobic culture (Systma, 2006). At first glance, Sytsma's argument might appear to be in the patient's best interest, especially in a country such as Iran where homosexuality is punishable by death. Still, it is ethically untenable for physicians to participate in sexual-orientation engineering. This is especially true given the troubling history of American clinical interventions to curb homosexuality, such as electroshock therapy, castration, lobotomies, hormone therapy (Swartz, 2011), and nausea-inducing drugs (James, 2011). And "reparative" therapy—psychological therapy intended to change sexual orientation—has been shown to cause significant emotional harm to patients, often inducing depression and suicide attempts (Associated Press, 2009). Furthermore, scientific knowledge about the specific genetic, biological, and environmental factors influencing sexual orientation is nebulous to begin with, making any kind of informed medical decision-making problematic (Langstrom, Rahman, Carlstrom, & Lichtenstein, 2010). All in all, then, attempts to manipulate sexual orientation in intersex patients are historically insensitive, an ethical abrogation of human rights, emotionally detrimental to the patient, and scientifically hazy.

In making her argument, Sytsma contends that "changing the boy is certainly more within our power than changing his culture, and the surgeries will make it easier for him to thrive in that culture" (Systma, 2006). However, the family and the patient retain the choice of moving to a more accepting social environment at a later date if the child indeed does identify as homosexual. Specifically, the United States (Bilefsky, 2011) and Great Britain ("Two Gay Men," 2010) grant asylum based on persecution due to sexual orientation, though the asylum process is often extremely long, arduous, and full of uncertainty (Bilefsky, 2011). It is myopic to allow ever-changing social conditions such as homophobia significantly to affect gender assignment and clinical decision-making. Attitudes toward homosexuality in the U.S. have drastically shifted in recent years. NORC/University of Chicago data indicate that in 1973, 69.7% of

polled adults believed homosexual relations were always wrong, and this number fell to 43.5% in 2010 (Smith, 2011). This public-opinion shift is exemplified by the U.S. Supreme Court's June 2013 ruling declaring the Defense of Marriage Act unconstitutional (Schwartz, 2013). While homosexuality remains socially stigmatized and often illegal in the Arab world, this attitude is not necessarily impervious to change. Brian Whitaker, a former Middle East editor of the *Guardian* and author of the book *Unspeakable Love: Gay and Lesbian Life in the Middle East,* explains:

Well, I still like to think that probably attitudes will change at some time in the not too distant future. I mean, I think you have to look at the way satellite TV and the Internet are affecting people in the region. They're getting information from outside the region that they wouldn't have had in the past, and I think gradually this is beginning to change attitudes, particular[ly] among the educated young people in some of the big cities. (CNN Transcripts, 2006)

## CONCLUSION

Physicians involved in intersex clinical management have a responsibility to respect patient autonomy, patient disclosure, and informed consent. They also have an ethical obligation to pursue the patient's best interests while promoting universal human rights. This obligation requires the physician to be concerned primarily with promoting concordance between the child's assigned gender and his or her likely future gender identity, in order to minimize the risk of gender dysphoria. Local cultural factors such as economics, politics, and homophobia simply have no place in clinical decision-making.

I thus embrace ethical universalism in intersex clinical management. While physicians must remain culturally sensitive to local values, such sensitivity cannot fundamentally impinge on universal truths and human rights. In undertaking ethical decision-making, physicians must balance the benefits and harms to the patient within the local milieu. In this case, the potential distress posed by gender dysphoria ultimately outweighs any local cultural benefits gained by being assigned a specific gender or sexual orientation.

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# Mineral and Bone Metabolism Disorders in Minority Incident ESRD Patients in an Inner-City Hemodialysis Unit

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**Background:** Chronic kidney disease (CKD) predisposes patients to mineral and bone metabolism disorder (CKD-MBD), which is a well-known risk factor for increased mortality. Because Medical Evidence Form 2728 from the Centers for Medicare and Medicaid Services for incident end-stage renal disease (ESRD) patients does not require documentation of CKD-MBD markers, MBD status on incident patients remains unknown.

**Objective:** Retrospective observational study to determine the prevalence of mineral and bone metabolism disorder in minority incident ESRD patients.

**Methods:** We studied all incident ESRD patients in our hemodialysis unit between January 2000 and September 2008. Patients followed for less than three months were excluded. Target values for CKD stage 5 were defined as per 2003 Kidney Disease Outcome Quality Initiative guidelines.

**Results:** One hundred seventy-four patients were studied, with a mean age of 53.7±16.1 years, mean body mass index of 26.67±5.98 kg/m$^2$, and mean estimated glomerular filtration rate of 6.7±4.03 mL/min/1.73m$^2$. Mean lab values with one standard deviation were as follows: corrected calcium 8.5±1.3 mg/dL, serum albumin 3.05±0.77 g/dL, phosphorus 5.5±2.2 mg/dL, calcium-phosphorus product 46.7±18.5 mg$^2$/dL$^2$, and intact parathyroid hormone (iPTH) 440.9±397.8 pg/mL. Target values for calcium, phosphorus, calcium-phosphorus product, and iPTH were met in 34%, 42%, 72%, and 31% of the patients, respectively, while only 6% of the patients met all four target values.

**Conclusions:** CKD-MBD is widely prevalent in minority incident dialysis patients at initiation of therapy. Its management continues to be a challenge and warrants early recognition and therapy in CKD patients.

## INTRODUCTION

Chronic kidney disease (CKD) is widely prevalent in the United States, with a rate of 16.8% in adults over the age of 20 (*MMWR Weekly,* 2007). It has been associated with significantly increased all-cause and cardiovascular mortality (Tonelli et al., 2006). The disease predisposes patients to significant alteration in mineral and bone metabolism, which is now known as mineral and bone disorder (CKD-MBD). CKD-MBD starts early during the course of CKD and becomes increasingly prevalent as the disease progresses (Martin et al., 2007). CKD-MBD has been well recognized as a risk factor for increased morbidity, hospitalization, all-cause mortality, and cardiovascular mortality among CKD and end-stage renal disease (ESRD) patients (Block, Hulbert-Shearon, Levin, & Port, 1998; Ganesh, Stack, Levin, Hulbert-Shearon, & Port, 2001; Tentori et al., 2008; Wald et al., 2008). Studies conducted so far have primarily focused on prevalent ESRD patients (Table 1) regarding MBD markers and achievement of Kidney Disease Outcome Quality Initiative (K/DOQI) targets (Block et al., 1998; Young et al., 2004; Yokoyama et al., 2004; Al Aly, Gonzalez, Martin, & Gellens, 2004; Maduell, Gorriz, Pallardo, Pons, & Santiago, 2005; Mahdavi-Mazdeh, Zamyadi, Norouzi, & Heidary Rouchi, 2007). Only a few studies on CKD-MBD markers have targeted the incident ESRD population (Tangri et al., 2011; Danese, Belozeroff, Smirnakis, & Rothman, 2008; Melamed et al., 2006), but data on minority patients are lacking. Minorities receive less pre-ESRD care and are more likely to be initiated on maintenance dialysis at more-advanced stages of CKD. Because Center for Medicare and Medicaid Services (CMS) Medical Evidence Form 2728 for incident ESRD patients does not require reporting of CKD-MBD indicators, complete data on MBD status in minority incident patients remain inaccessible. We conducted a retrospective cross-sectional study to determine the MBD status of minority incident ESRD patients.

## METHODS

We conducted a retrospective observational study on 174 incident ESRD patients who initiated hemodialysis at the Lincoln Medical and Mental Health Center hemodialysis unit between January 2000 and September 2008. Our hemodialysis unit, serving a predominantly minority population, is an inner-city, hospital-based unit; all patients were started on dialysis in the hospital. Patients' baseline data were collected from CMS Medical Evidence Form 2728 and electronic medical records. Laboratory data from within 15 days of the initiation of dialysis were collected. Patients followed for less than three months after dialysis initiation were excluded because of the possibility of renal recovery during that period.

It was our standard practice to check for MBD markers at or prior to initiation of hemodialysis. Calcium level was corrected for serum albumin using the formula of observed

**Table 1 | National and International Experiences in Prevalent ESRD Patients Regarding CKD-MBD Markers**

| CKD Stage 5 Target Values | DOPPS I (1998) | DOPPS II (2004) | Yokoyama et al. (2004) | Al Aly et al. (2004) | Maduell et al. (2005) | Mahdavi-Mazdeh et al. (2007) |
|---|---|---|---|---|---|---|
| Calcium (8.4–9.5 mg/dL) | 40.5% | 42.5% | 49% | 49% | 45% | 53.2% |
| Phosphorus (3.5–5.5 mg/dL) | 40.8% | 44.4% | 50% | 36% | 55% | 52.2% |
| Calcium x Phosphorus (<55 $mg^2/dL^2$) | 56.5% | 61.4% | — | 57% | 73% | 75.1% |
| iPTH (150–300 pg/mL) | 21.4% | 26.2% | 27% | 20% | 26% | 27.7% |
| All Four Target Values Met | 4.6% | 5.5% | 9% | 7% | 7.3% | 1.8% |

**Table 2 | Patients' Baseline Characteristics**

| | Our Study Population | USRDS (2000–2006) | p-value |
|---|---|---|---|
| **Total Patients** | **n=174** | **n=709,212** | **—** |
| Female | 89 (51.1%) | 45.4% | 0.14 |
| Hispanic | 116 (66.7%) | 13.2% | <0.0001 |
| African American | 49 (28.1%) | 28% | 0.96 |
| Asian | 9 (5.2%) | 2.6% | 0.05 |
| Mean Age (years) | 53.7±16.1 | 62.8 | 0.001 |
| Mean eGFR ($mL/min/1.73m^2$) | 6.7±4.03 | 9.9 | 0.001 |
| Mean BMI ($kg/m^2$) | 26.67±5.98 | 27.7 | 0.02 |
| ESRD Etiology | | | |
| Diabetes Mellitus | 39.1% | 44.8% | 0.14 |
| Hypertension | 20.1% | 27.4% | 0.03 |
| Chronic Glomerulonephritis | 19.5% | 9.9% | <0.0001 |
| HIV Nephropathy | 3.4% | 0.8% | 0.0005 |
| Polycystic Kidney Disease | 2.3% | 2.2% | 0.9 |
| Obstructive Uropathy | 2.3% | — | — |
| Other | 13.3% | 14.9% | 0.6 |

calcium + 0.8 x (4.0 - serum albumin [g/dL]). Corrected calcium was used to calculate calcium-phosphorus product. Glomerular filtration rate (GFR) was estimated with the modification of diet in renal disease formula (Levey et al., 1999). Target values of MBD markers for CKD stage 5 were established per K/DOQI guidelines (calcium 8.4–9.5 mg/dL, phosphorus 3.5–5.5 mg/dL, calcium-phosphorus product less than 55 $mg^2/dL^2$, and intact parathyroid hormone [iPTH] 150–300 pg/mL) (*K/DOQI Clinical Practice Guidelines,* 2003).

### Statistical Analysis

Data were analyzed using a two-tailed Student's t-test, chi square test, logistic regression analysis, and analysis of variance (ANOVA). A p-value of less than 0.05 was considered statistically significant. We also analyzed the trend of achievement of target CKD-MBD marker values between the years 2000 and 2008 by dividing the time period into two-year intervals. We attempted to assess the impact of the K/DOQI guidelines publication in our study population. All analyses were performed with Stata Version 11.2 (Stata Corp., Odessa, TX). The study protocol was reviewed and approved by our Institutional Review Board.

## RESULTS

One hundred seventy-four patients were included in the study, with a mean age of 53.7±16.1 years, mean body mass index (BMI) of 26.67±5.98 $kg/m^2$, and mean estimated

**Table 3 | Mean Values of CKD-MBD Markers in Pre- and Post-K/DOQI Guidelines**

| MBD Markers | Pre-K/DOQI | Post-K/DOQI | p-value |
|---|---|---|---|
| Calcium (mg/dL) | 8.6±1.2 | 8.4±1.3 | 0.2 |
| Phosphorus (mg/dL) | 5.4±2.2 | 5.7±2.1 | 0.28 |
| iPTH (pg/mL) | 377±307 | 523±480 | 0.01 |
| Calcium x Phosphorus ($mg^2/dL^2$) | 45.7±19 | 47.4±17.8 | 0.55 |

GFR (eGFR) of 6.7±4.03 mL/min/1.73$m^2$. Hispanic, African American, and Asian ethnicity made up 66.7%, 28.1%, and 5.2% of the studied patients respectively. Table 2 summarizes patients' baseline characteristics compared with United States Renal Data System (USRDS) incident ESRD patients from 2000 to 2006 (U.S. Renal Data System, 2008). Health coverage was as follows: Medicaid, 36%; Medicare, 13%; both Medicaid and Medicare, 16%; other, 3%. Thirty-two percent of patients were without any coverage. Most patients were unemployed (82%) or retired (11% due to age and 1% due to disability).

Mean lab values with one standard deviation in incident ESRD patients were as follows: albumin 3.05±0.77 g/dL, calcium 8.5±1.3 mg/dL, phosphorus 5.5±2.2 mg/dL, iPTH 440.9±397.8 pg/mL, and calcium-phosphorus product 46.7±18.5 $mg^2/dL^2$. The impact of the K/DOQI guidelines was assessed as shown in Table 3. We compared mean values of CKD-MBD markers before December 31, 2003, and after January 1, 2004 (three months after the guidelines were published in October 2003), and found no difference, aside from higher iPTH levels in the post-K/DOQI era.

Figure 1 shows trends of proportions of patients achieving target CKD-MBD markers over eight years. Target value for the calcium-phosphorus product was achieved in 65% to 77% of the patients, whereas the other CKD-MBD marker targets were met in only 28% to 45% of the patients. Logistic regression analysis showed trends to be nonsignificant for all values. Similarly, trends of CKD-MBD marker mean values over the years were nonsignificant as analyzed by ANOVA (Figures 2A–C).

The target calcium value was met in 34% of the patients, while 45% of the patients had calcium less than 8.4 mg/dL and 21% of the patients had calcium greater than 9.5 mg/dL. The target value of phosphorus was met in 42% of the patients, while 16% of the patients had phosphorus less than 3.5 mg/dL and 42% of the patients had phosphorus greater than 5.5 mg/dL. Seventy-two percent of the patients had calcium-phosphorus product in the target range, while 28% of the patients had an elevated calcium-phosphorus product of greater than 55 $mg^2/dL^2$. The target iPTH level was met in 31% of the patients, while an iPTH level of <150 pg/mL was seen in 17% of the patients. An elevated iPTH level of greater than 300 pg/mL was seen in 52% of the patients.

Only 6% of the patients met all four target values. Age, gender, ethnicity, and BMI did not have a statistically significant impact on the achievement of target CKD-MBD marker values, except that patients with calcium within the target range were significantly older than patients with calcium less than 8.4 mg/dL (57.5±17.9 years vs. 51.3±14.9 years, p-value = 0.03).

## DISCUSSION

Results of our study showed that there were no significant changes in the trends of CKD-MBD markers and the proportion of patients achieving target values in minority incident ESRD patients over the years of our study. The introduction of the K/DQOI guidelines also did not result in significant improvement in mean values of CKD-MBD markers; we found significantly higher iPTH values after the publication of the guidelines.

Our patients were significantly younger compared with the national average and had lower eGFR at initiation of dialysis and lower BMI, but they also had a significantly higher proportion of HIV nephropathy and chronic glomerulonephritis as the etiology of ESRD. Lower eGFR at dialysis initiation likely reflects late presentation for medical care in our population. The remaining comorbidities were comparable.

Our study population consists predominantly of minorities and is considerably different from the USRDS population, with a significantly higher proportion of Hispanics. Minorities constitute about one third of the U.S. population, with Hispanics being the largest minority group. Minority populations tend to be poorer and have less education, and

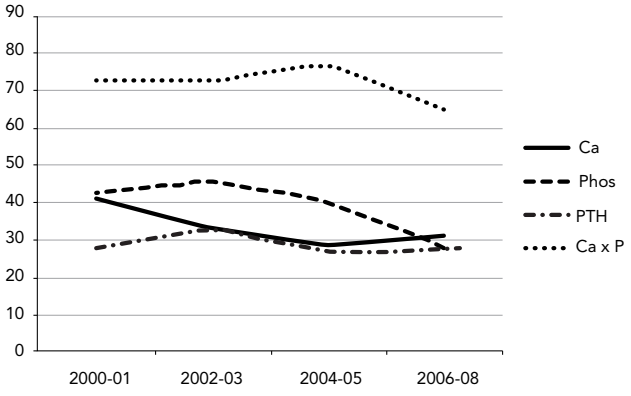


**Figure 1 | Percentage of patients achieving CKD-MBD targets.** p > 0.05 (nonsignificant) for all trends

they are more likely to lack health insurance coverage and to suffer from a severe disease burden. These factors could be significant barriers to obtaining appropriate healthcare in our patient population. According to 2011 U.S. Census Bureau data, 30.1% of Hispanics and 19.5% of blacks were without health insurance (U.S. Census Bureau, 2011). Eighty-two percent of our patients were unemployed, and 32% of our patients were without any medical coverage. According to the USRDS, in 2005–2007, 20.2% of incident ESRD patients were unemployed and 7.6% were without health insurance (U.S. Renal Data System, 2012). MBD is widely prevalent in minority incident ESRD patients, which could be due to lack of pre-ESRD care and lack of health insurance, and may be related to unemployment, poor socioeconomic status, or poverty.

Nephrologists have to complete CMS Medical Evidence Form 2728 upon initiation of maintenance dialysis. The requested information includes all demographic data, comorbid conditions, and laboratory values except CKD-MBD markers. Thus, the nationwide prevalence of CKD-MBD abnormalities at initiation of dialysis remains undetermined. Only recently have CMS guidelines mandated monitoring of CKD-MBD markers in ESRD patients.

To our knowledge, ours is the first study reporting the status of mineral and bone metabolism markers and achievement of target values in minority incident ESRD patients. Dialysis Outcomes and Practice Patterns Study (DOPPS) data reported on the achievement of target values for CKD-MBD in prevalent ESRD patients only (Mahdavi-Mazdeh et al., 2007).

According to DOPPS II data, target calcium, phosphorus, calcium-phosphorus product, and iPTH values were met in 42.5%, 44.4%, 61.4%, and 26.2% of prevalent ESRD patients, respectively, in the United States. These targets were met in 34%, 42%, 72%, and 31% of incident ESRD patients, respectively, in our study population. All four targets were met in only 5.5% of DOPPS II prevalent ESRD and 6% of our incident ESRD patients. It should be noted that these comparisons are not among similar patient populations, as these similar proportions of patients achieving target CKD-MBD marker values represent widely heterogeneous ESRD subsets in each study group.

Major features of deranged mineral and bone metabolism include hypocalcaemia, hyperphosphatemia, secondary hyperparathyroidism, altered Vitamin D metabolism, bone disease, soft-tissue calcification (including coronary artery and cardiac valves), pruritus, proximal myopathy, calciphylaxis, skin ulceration, and soft-tissue necrosis (*K/DOQI Clinical Practice Guidelines,* 2003). Abnormalities in arterial stiffness have been shown to be important mediators of cardiovascular events in patients with CKD (Block & Port, 2003). Hyperphosphatemia is associated with higher fracture risk (Block et al., 2004), increased pulse pressure (Klassen et al., 2002), increased risk of all-cause mortality (Ganesh et al., 2001; Wald et al., 2008; Block et al., 2004), cardiovascular mortality (Block et al., 1998; Ganesh et al.,

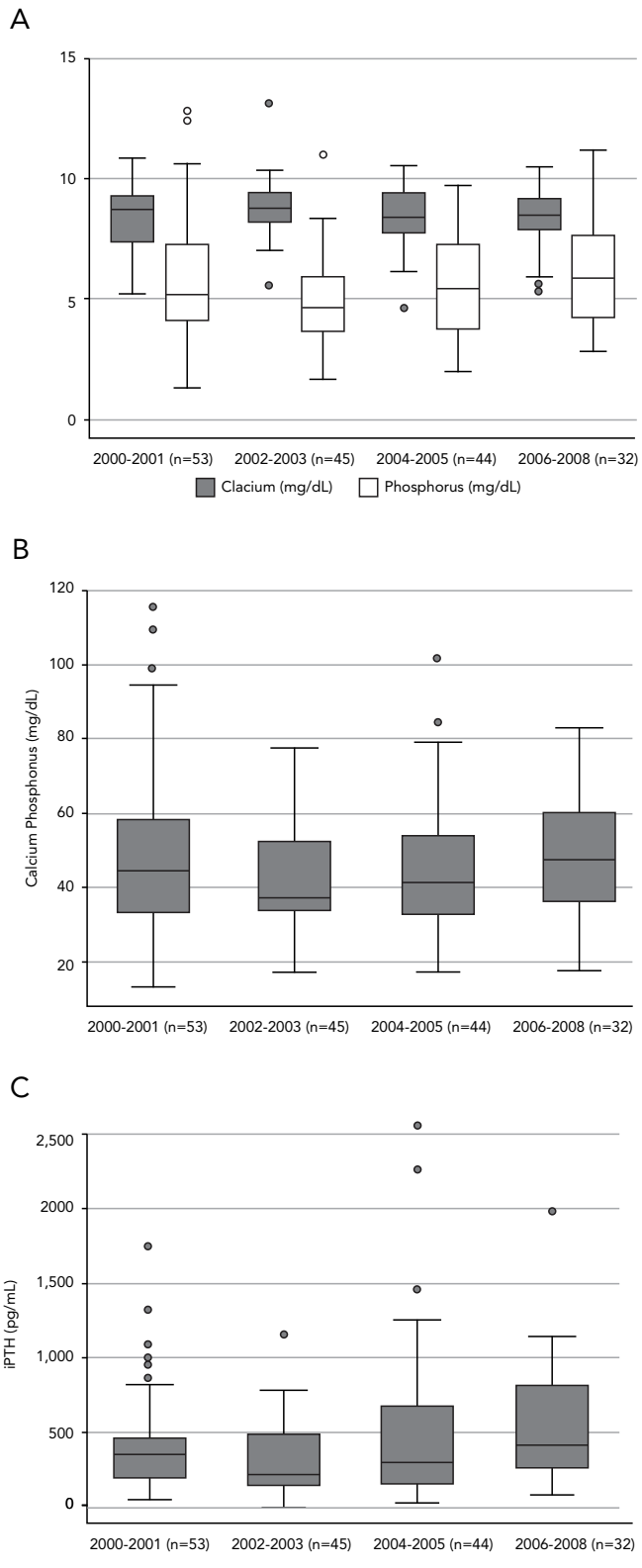


**Figure 2 | Trends of levels of CKD-MBD markers**. (A) Trends of levels of calcium and phosphorus. (A-C) P > 0.05 (nonsignificant) for all trends. (B) Trends of levels of calcium x phosphorus product . (C) Trends of levels of iPTH.

2001; Young et al., 2005), infection-related mortality, and sudden death (Ganesh et al., 2001).

An analysis of the United Kingdom Renal Registry by Tangri et al. (2011) including incident ESRD patients between January 2002 and December 2004 showed target achievement among patients for calcium (43–47%), phosphorus (54–62%), and iPTH (23-26% ), and did not find a benefit of achievement of K/DOQI targets in decreasing all-cause mortality. In contrast, the study by Danese et al. (2008) of incident ESRD patients between July 2000 and June 2002 showed consistent achievement of CKD-MBD targets to be a strong predictor of survival.

Block et al. (2004) showed population-attributable risk of all-cause mortality in CKD stage 5 to be 17.5% for MM mineral metabolism abnormalities (phosphorus greater than 5.0 mg/dL, calcium greater than 10 mg/dL, iPTH greater than 600 pg/mL), 11.3% for anemia (hemoglobin less than 11 gm/dL), and 5.1% for insufficient dialysis (urea reduction ratio less than 65%). Their study highlights the impact of mineral and bone metabolism disorders on mortality in advanced CKD compared with anemia and inadequate dialysis, which was the main focus until recently. Presently, the beneficial effect of achieving CKD-MBD markers is demonstrated only by observational studies. Various organizations around the world set forth guidelines for MBD in advanced CKD that were most recently updated by KDIGO (Kidney Disease: Improving Global Outcomes) in 2009.

Our study cohort differs in racial and ethnic makeup from the overall ESRD population of the United States. However, this difference has the potential to highlight disparities in care among those at greatest risk for complications because of socioeconomic factors. Our study had a small sample size and we lacked data on pre-ESRD care and outcomes such as mortality, which would have improved our understanding of the impact of achieving target CKD-MBD markers. We also lack information on the use of phosphate binders and vitamin D analogues in our study population.

## CONCLUSION

Our study demonstrated that mineral and bone metabolism abnormalities are widely prevalent in minority incident ESRD patients, and only 6% of the patients achieved target values for all MBD markers at the time of initiation of dialysis. This finding may be explained by lack of pre-ESRD care in our minority population. Estimating CKD-MBD status at the initiation of dialysis and including MBD indicators on the CMS medical evidence form will help ascertain the magnitude of MBD in ESRD patients. Early referral to nephrology and early recognition and management of CKD-MBD as per the guidelines may affect morbidity and mortality related to these disorders.

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# Preemptive Use of Eculizumab for Living-Donor Kidney Transplantation in a Child with Atypical Hemolytic Uremic Syndrome

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Eculizumab is an anti-complement C5 monoclonal antibody that has recently been reported as an effective therapy for atypical hemolytic uremic syndrome. However, few data are available on the preemptive use of this medication in pediatric kidney transplantation. This report describes a successful preemptive use of eculizumab in combination with living unrelated kidney transplantation in a 10-year-old child with end-stage renal disease secondary to atypical hemolytic uremic syndrome who has a complement factor H mutation that has not been previously reported. Further observations and clinical trials are required to address the challenges and areas of uncertainty related to preemptive eculizumab therapy for kidney transplantation in children and adults with atypical hemolytic uremic syndrome.

## INTRODUCTION

Atypical hemolytic uremic syndrome (aHUS) is a rare thrombotic microangiopathy characterized by overactivation of the alternative complement pathway. This syndrome is associated with severe clinical manifestations, a tendency to recur, and, until recently, a poor long-term prognosis (Noris & Remuzzi, 2009). With conventional supportive therapy, the expected rate of graft failure after kidney transplantation due to recurrent aHUS among patients with a mutation in a complement gene ranges from 50% to 80% within the first five years post transplant (Le Quintrec et al., 2013; Zimmerhackl, Scheiring, Prufer, Taylor, & Loirat, 2007).

Eculizumab is a high-affinity humanized recombinant IgG2/IgG4 monoclonal antibody against the complement component 5 (C5). This medication has recently emerged as a promising agent for the treatment of alternative complement pathway activation disorders. In 2011, the Food and Drug Administration approved eculizumab for use in pediatric patients with aHUS. However, experience using eculizumab in pediatric kidney transplantation remains limited (Barnett et al., 2013; Krid et al., 2012; Nester et al., 2011; Weitz, Amon, Bassler, Koenigsrainer, & Nadalin, 2011; Zuber, Le Quintrec, et al., 2012). Particularly little is known about the preemptive use of this agent in initial living-donor kidney transplantation in pediatric recipients with aHUS.

## CASE

At age 5, the patient presented to the emergency department with complaints of fatigue, muscle weakness, pallor, and vomiting without diarrhea. His blood pressure was elevated and laboratory data showed serum creatinine 135.2 µmol/L (1.53 mg/dL), hemoglobin 4.50 g/dL, white blood cell count 15.7 x $10^9$/L, platelet count 76 x $10^9$/L, and reticulocyte count 15.8%. A peripheral blood smear showed schistocytes, helmet cells, and reticulocytes. Serum complement C3 level was decreased.

The patient was diagnosed with aHUS, was treated initially with plasma infusions, and was then treated with plasmapheresis. However, the patient's renal function deteriorated, and by age 6 the patient required chronic hemodialysis via an arteriovenous fistula. A kidney biopsy performed at that time showed vascular changes consistent with thrombotic microangiopathy and hypertension. Factor H analyses were performed at the Mario Negri Institute for Pharmacological Research in Bergamo, Italy. Sequencing of short consensus repeat (SCR) 20, a mutation hot-spot region of the factor H gene, revealed no mutations. Other SCRs were then sequenced, and a heterozygous mutation in SCR 15 was found (SCR 15: c.2831T>C, p. Trp920Arg). This mutation has not been previously reported and its pathogenicity has not yet been proven. Serum complement profile at the time of genetic analysis showed normal levels of factor H (512.82 mg/dL, normal range 350–750 mg/dL), C3 (126 mg/dL), and C4 (35 mg/dL). Other major genes associated with aHUS were analyzed, including complement factor I, membrane cofactor protein, complement factor B, and thrombomodulin, and no mutations were found. The ADAMTS13 level was normal at 37%, and no anti-ADAMTS13 antibodies were identified.

The patient remained on chronic hemodialysis in combination with plasma therapy, but he continued to exhibit severe hypertension and had two episodes of seizures and encephalopathy. Although the MRI findings were consistent with posterior reversible encephalopathy syndrome, a thromboembolic etiology of the encephalopathy was not completely excluded. In addition, the patient had an epi-

**Table 1 | Parameters of complement system and related laboratory values prior to eculizumab administration. Data shown for the initial seven doses.**

| | C5 Functional Assay | AH50 | CH50 | C3 | C4 | LDH | Hapto-globin | Hemoglobin |
|---|---|---|---|---|---|---|---|---|
| **Normal range / units** | 137–37900 U/ml | 75–170% | 31–60 U/ml | 70–245 mg/dL | 16–56 mg/dL | 120–325 U/L | 25–200 mg/dL | 10.9-13.3 g/dL |
| **Pre transplant*** | | | | | | | | |
| Dose 1 (day -7) | 17638 | 98 | 44 | 74 | 20 | 245 | 47 | 9.5 |
| Dose 2 (day -1) | <10 | <10 | <10 | 65 | 20 | 140 | 106 | 9.1 |
| **Post transplant** | | | | | | | | |
| day +1 | <10 | <10 | <10 | 58 | 12 | 226 | 95 | 7.3 |
| Dose 3 (day +7) | — | <10 | <10 | 109 | 23 | 270 | — | 7.2 |
| Dose 4 (day +14) | <10 | <10 | <10 | — | — | 201 | 194 | 9.1 |
| Dose 5 | — | <10 | <10 | 137 | 26 | 213 | 146 | 11.7 |
| Dose 6 | <10 | <10 | <10 | 131 | 22 | — | 93 | 12.1 |
| Dose 7 | <10 | <10 | <10 | 127 | 50 | — | 96 | 12.5 |

* Laboratory test samples were drawn before plasma therapy and before eculizumab.

sode of pulmonary edema without signs of fluid overload. The echocardiogram showed left-ventricle dilatation and hypertrophy with diminished systolic function and moderate mitral regurgitation. Of note, the serum troponin level was elevated at 1.85 µg/L (N<0.08 µg/L). The patient was placed on the deceased-donor waiting list for a combined liver-kidney transplant at his home institution. However, no suitable donor became available.

At age 10, the patient was referred to our institution for evaluation for a living-donor kidney transplant. At that time, his height was 126 cm and estimated dry weight was 24.5 kg, both below the 1st percentile for his age (Z-scores -1.81 and -1.85, respectively) despite nutritional support and recombinant growth hormone therapy. The patient was deemed eligible for a nonrelated living-donor kidney transplant with the preemptive use of eculizumab. Prior to transplantation, the patient was fully immunized, including with the meningococcal vaccine.

The University of Iowa protocol (Nester et al., 2011) was followed for the administration of eculizumab. On days -7 and -1 prior to the transplantation, the patient received plasmapheresis with 1.5 volumes of fresh frozen plasma. This was followed by eculizumab, 600 mg. (induction dose for body weight between 20 kg and 30 kg), diluted to a concentration of 5 mg/ml, over 35 minutes. The patient tolerated both therapies well. Laboratory assessment of the patient's complement system before and after treatment with eculizumab is shown in Table 1.

Nonrelated living-donor kidney transplantation was performed without perioperative complications. The donor was a 23-year-old male who was T- and B-cell compatible with the recipient. The donor was a 5 antigen mismatch to the recipient. The recipient's panel reactive antibodies were 0% and there were no donor-specific antibodies. Induction immunosuppression consisted of thymoglobulin and methylprednisolone. Triple maintenance immunosuppression included tacrolimus, mycophenolate mofetil, and prednisone. The patient had urine output immediately after the operation and by post-transplant day 2, the serum cre-

atinine was 53.04 μmol/L (0.6 mg/dL). The patient received two weekly doses of eculizumab, and thereafter was placed on an every-other-week maintenance regimen. We observed an initial decrease in the serum complement C3 level after the first dose of eculizumab, which persisted in the immediate post-transplant period but normalized about one month after transplantation (Table 1). Plasma therapies were not used during or after transplantation.

Two months after transplantation, the patient returned to his home institution, where he continues to receive eculizumab infusions every other week. At nine months' follow-up, his renal function remained stable, and there was no clinical or biochemical evidence of aHUS recurrence.

## DISCUSSION

Until recently, there were few therapeutic options in the treatment of children with end-stage renal disease (ESRD) secondary to aHUS. In most cases, treatment was limited to chronic dialysis. Isolated kidney transplantation has a high rate of recurrence, and combined liver-kidney transplantation, while potentially curative for the underlying genetic defect, poses a high risk for mortality. Most children with aHUS and ESRD require, in addition to dialysis, chronic plasma therapy to prevent extrarenal manifestations of aHUS. In the case of our patient, his extrarenal complications could have been explained by alternative complement pathway activation. This included two occurrences of encephalopathy and the episode of severe ventricular dysfunction in combination with respiratory insufficiency.

A number of pathogenic mutations in the SCR 15 region of the complement factor H gene have been identified (Bresin et al., 2013). However, to our knowledge, the mutation found in our patient (SCR 15: c.2831T>C) has not been previously reported, and its pathogenicity has not yet been demonstrated. In view of his normal factor H level, it does not appear that the mutation in our patient is associated with a quantitative factor H deficiency, and therefore a functional defect may be expected; however, a functional analysis of factor H has not been performed.

Donor selection is a challenge for children with aHUS and ESRD. Living related donation is usually not an option due to a high level of pathogenic genes encoding alternative complement pathway components carried in the families of these patients. In our case, we did not offer genetic testing to the family members because of financial considerations and because a negative test result cannot exclude the possibility of another causative genetic defect either not yet discovered or not covered by testing. Therefore, genetic testing is not capable of identifying relatives as suitable candidates for kidney donation. Adverse outcomes for both the recipient and the donor after kidney donation by a family member to a child with aHUS have been described (Donne et al., 2002).

Despite promising reports, many questions regarding the preemptive use of eculizumab in renal transplantation remain unanswered. These include the utility of pretransplant plasmapharesis, optimization of the eculizumab dosage before and after transplantation, treatment regimens for deceased versus nonrelated living-donor transplants, the optimal induction and maintenance of immunosuppression, laboratory criteria for complement blockage under eculizumab, and the length and cost of the treatment with this agent.

In our case, we used preemptive plasmapheresis before eculizumab infusions as per the University of Iowa protocol (Nester et al., 2011). However, other investigators suggest that eculizumab without plasma therapy may be sufficient to prevent aHUS recurrence (Krid et al., 2012; Roman-Ortiz et al., 2014; Weitz et al., 2011). We used eculizumab on days -7 and -1 prior to the transplantation. But even after the first dose of eculizumab, the functional activity of the terminal complement components was fully suppressed (Table 1). This is consistent with data indicating that complement blockade is complete as soon as one hour after the first eculizumab infusion. Effective treatment with a single dose of eculizumab before surgery has been reported (Krid et al., 2012; Roman-Ortiz et al., 2014). Administration of eculizumab within the first 24 hours after surgery is currently recommended due to possible complement activation after kidney reperfusion and surgical trauma. Disease exacerbation in the immediate postoperative period has been documented when eculizumab was not administered within the first day post transplant (Ranch, Crowther, Arar, & Assanasen, 2014). Blockade of the alternative pathway above the C5 step is not expected after eculizumab treatment. Additionally, similar changes in C3 levels observed in our patient after eculizumab treatment have also been reported in other pediatric cases (Nester et al., 2011; Weitz et al., 2011); however, they are not well understood. Finally, we chose thymoglobulin for induction immunosuppression, but successful use of basiliximab in patients with aHUS has also been described (Nester et al., 2011; Roman-Ortiz et al., 2014).

The advantages of eculizumab over previously available standards of care are obvious. The use of this agent reduces central line-related complications associated with plasmapharesis. Additionally, eculizumab improves renal survival, thus reducing kidney transplantation failure due to aHUS recurrence and preventing the need for chronic dialysis. Together, the benefits of eculizumab treatment contribute to improved quality of life and allow parents and children to go about their lives. However, the financial burden associated with maintenance eculizumab therapy is an important issue, especially in resource-limited countries. Depending on the size of the child, the annual cost of standard maintenance treatment may vary from around $100,000 to more than $500,000, making eculizumab one of the most expensive lifelong medical treatments (Zuber, Le Quintrec, et al., 2012). This and other concerns prompted some to consider the possibility of discontinuing eculizumab therapy with strict home monitoring for early signs of relapse in patients with aHUS who achieve stable remission (Ardissino et al., 2014).

Eculizumab appears to be an effective agent for preemptive therapy in nonrelated living-donor kidney transplantation in patients with aHUS. However, current protocols for the prophylactic use of eculizumab in renal transplantation are empirical. More observations are required to develop the most effective and cost-efficient approach to the use of this agent. Incorporating cases of this kind into the national registry may help optimize treatment strategies.

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# An Unusual Case of Drug-Induced Acute Pancreatitis

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We report a rare case of drug-induced pancreatitis in a patient receiving repaglinide antidiabetic therapy. A patient with type 2 diabetes mellitus presented with severe abdominal cramping, nausea, and vomiting. Three months prior to symptoms, repaglinide was added to the patient's current regimen of metformin. The patient was diagnosed with acute pancreatitis, treatment was initiated, and repaglinide was discontinued. There was no history of pancreatitis or other risk factors such as history of gallstones, alcohol abuse, or hypertriglyceridemia. The patient reported resolution of symptoms following discontinuation of repaglinide. Considering the temporal relationship of his symptoms to the addition of repaglinide to his existing antidiabetic regimen, this case strongly suggests a possible causal link between repaglinide and the etiology of acute pancreatitis in this patient.

## INTRODUCTION

Oral insulin secretagogues are antidiabetic medications that have been reported to be causally linked to acute pancreatitis (Blomgren & Sudstrom, 2002). Meglitinides are a class of insulin secretagogues that act in a glucose-dependent manner to increase pancreatic insulin secretion. They work specifically by closing adenosine triphosphate (ATP)-dependent potassium channels on the β-cell, causing calcium channels to open and thereby increasing calcium influx and insulin secretion (Stein, Lamos, & Davis, 2013). We will consider the effects of a meglitinide analog, repaglinide, by presenting a case of likely drug-induced pancreatitis in a patient who was started on repaglinide.

## CASE PRESENTATION

A 40-year-old male with a medical history of type 2 diabetes mellitus, diabetic nephropathy, obesity, and hypertension presented to the emergency room with two weeks of severe, cramping epigastric pain that radiated to the back. Pain was intermittent, severe, and associated with nonbilious, nonbloody vomiting and nonbloody diarrhea. The patient denied a history of gallstones, hypertriglyceridemia, pancreatitis, recent alcohol consumption, fevers, night sweats, or weight loss. His medication regimen included metformin 500 mg PO BID, lisinopril, and metoprolol XL, as well as repaglinide 2 mg PO before each meal, which had been initiated three months earlier for optimal glycemic control. On admission, vital signs were temperature of 98.5° F, blood pressure of 164/103 mmHg, pulse of 79 beats/minute, and respiratory rate of 20 breaths/minute. On abdominal exam, the left upper quadrant was tender, without rebound, guarding, or organomegaly. Sclera and skin were anicteric, and the remainder of the physical exam was unremarkable.

Laboratory analysis revealed serum lipase 132 U/L (reference range 16–58 U/L), amylase 19 U/L (reference range 34–131 U/L), glucose 423 mg/dL (reference range 74–200 mg/dL), creatinine 2.5 mg/dL (reference range 0.6–1.2 mg/dL), calcium 8.9 mg/dL (reference range 8.7–10.0 mg/dL), triglycerides 216 mg/dL (reference range <250 mg/dL), and HbA1c 12.3%. The remaining laboratory values, including white-blood-cell and liver-function tests, were unremarkable. Imaging was obtained, and abdominal computed tomography revealed focal pancreatitis around the head and uncinate of the pancreas (Figure 1). Abdominal ultrasound showed no evidence of cholelithiasis. The patient was diagnosed with acute pancreatitis, made NPO, and given IV fluids. An insulin sliding scale, morphine, and ondansetron were initiated, and repaglinide was stopped. On hospital day 3, the patient's symptoms resolved, and serum lipase and amylase decreased to 21 U/L and 16 U/L, respectively. He tolerated a PO diet and was discharged home symptom free, on metformin and insulin for glycemic control.

## DISCUSSION

To date, there are 525 different medications in the World Health Organization database that can induce acute pancreatitis (Nitsche, Jamieson, Lerch, & Mayerle, 2010). Overall, drugs remain a relatively rare causative factor for acute pancreatitis, with an incidence between 0.1% and 2% of pancreatitis cases (Nitsche et al., 2010). The elderly may be especially susceptible to drug-induced pancreatitis due to polypharmacotherapy and mixed drug interactions (Nitsche et al., 2010). Although we know that activation of trypsin can lead to pancreatic autodigestion and, consequently, acute pancreatitis, the mechanisms by which certain drugs can induce pancreatitis are not known (Blomgren & Sudstrom, 2002). One theory is that some drugs known to diffuse into the pancreas, such as metronidazole, can exhibit a direct toxic effect; another is that drugs can lead to an accumulation of toxic metabolites (Nitsche et al., 2010). Unfortunately, data for drug-induced pancreatitis remain sparse and most are collected from case reports and case-control studies.

A review of the literature shows that some antidiabetic medications have been linked to pancreatitis. In a case-control study, Blomgren and Sudstrom (2002) found an increased risk of first-time acute pancreatitis among diabetic patients taking glyburide. Insulin and long-term metformin

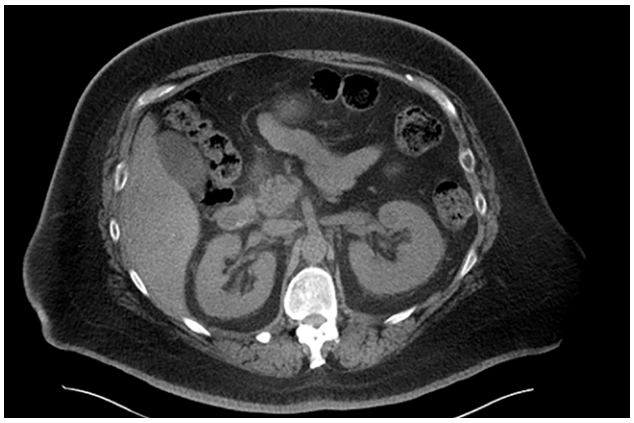

**Figure 1 | Focal pancreatitis around the head and uncinate of the pancreas.**

use were found to be associated with a decreased risk of acute pancreatitis. Long-term sulfonylureas, however, were found to increase this risk (Gonzalez-Perez, Schlienger, & Garcia Rodriguez, 2010). An analysis of the Food and Drug Administration's adverse-event reporting system by Elashoff, Matveyenko, Gier, Elashoff, and Butler (2011) found that two glucagon-like peptide-1 (GLP-1) agonists in particular, exenatide and liraglutide, carry a sixfold increased risk of pancreatitis compared with other therapies. Because of this correlation, as seen in several case reports, liraglutide is recommended to be used cautiously in diabetic patients with a history of pancreatitis (Franks, Lee, & George, 2012). In animal models, exenatide administration resulted in focal proliferation of the exocrine pancreas, which is a well-recognized component of chronic pancreatitis in humans (Gier et al., 2012). Similarly, Matveyenko et al. (2009) showed that rats treated with sitagliptin, another GLP-1 agonist, also had evidence of increased pancreatic ductal proliferation. Although a clear causal relationship between antidiabetic medications and pancreatitis has not yet been established, studies showing the temporal relationship of drug use and symptom onset, combined with resolution of symptoms following drug discontinuation, suggest that such an association cannot be excluded.

Our patient's history and clinical findings point to repaglinide as the etiologic agent of acute pancreatitis in this case. Though we cannot rule out an occult etiology for his condition, he had no major risk factors for pancreatitis. There are presently no previously reported cases of repaglinide-induced acute pancreatitis, and a plausible mechanism for antidiabetic drug–induced pancreatitis has yet to be found. Because initiation of repaglinide presumably corresponded to an episode of acute pancreatitis in our patient and discontinuation resulted in resolution of symptoms, repaglinide is strongly suggested to be the cause. This is an unusual and rare case of repaglinide-induced pancreatitis, and we recommend caution when prescribing repaglinide to patients with a history of pancreatitis. Physician recognition and patient awareness of possible side effects of repaglinide could decrease morbidity and shorten overall hospital stays.

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# Successful Endoscopic Clipping of Appendiceal Orifice Bleeding: A Technical Maneuver to Convert an Emergency to an Elective Procedure

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**Objective:** We report a rare case of an elderly man with appendiceal bleeding successfully treated with endoscopic placement of hemoclips.

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

**Results:** An 89-year-old man presented with two episodes of bloody diarrhea that occurred two hours apart. Colonoscopy revealed active bleeding from the appendiceal orifice. Hemostasis was achieved with epinephrine injections followed by placement of five hemoclips to effectively close the appendiceal orifice. An abdominal computed tomography (CT) showed an irregular thickening of the appendix wall, raising the possibility of an appendiceal mass. On hospital day 4, the patient underwent appendectomy and partial cecectomy. Pathology revealed focal ulceration of the mucosa without malignancy. The remainder of the patient's hospital course was uneventful.

**Conclusion:** The endoscopic methods used in our case proved effective in achieving hemostasis and allowed the patient to be stabilized prior to surgery. It is unclear whether longer monitoring would reveal any possible long-term complications after endoscopic closure of the appendix. It would be of interest to further investigate this approach to assess the long-term safety and efficacy of this procedure.

## INTRODUCTION

Gastrointestinal bleeding (GIB) is a common and potentially life-threatening condition that accounts for more than 300,000 hospitalizations per year (Lin & Rockey, 2005). Appendiceal hemorrhage is an extremely rare cause of GIB, with few cases reported in the scientific literature. We report a rare case of an elderly man with appendiceal bleeding and describe how hemostasis was successfully achieved with endoscopic placement of hemoclips.

## CASE

An 89-year-old Chinese-speaking man with a medical history of hypertension and a remote history of peptic ulcer disease presented with bloody diarrhea. He reported two episodes that occurred two hours apart, but denied having abdominal pain, preceding diarrhea, or recent illness. He reported no prior episodes of bloody diarrhea. His medications included daily aspirin and amlodipine. The patient reported having a normal colonoscopy three years earlier. On physical examination he was afebrile, with blood pressure 119/80 mmHg, pulse 113 beats/min, respiratory rate 22 breaths/min, and oxygen saturation 100% on room air. Abdominal exam was benign and digital rectal exam revealed bright red blood and prolapsed internal hemorrhoids. Initial laboratory data revealed hematocrit 44.1%, but two hours later the repeat hematocrit was 24.2%. The remainder of his physical exam and labs was unremarkable. Gastric lavage produced bilious, nonbloody aspirate. He was resuscitated with intravenous fluids and packed red blood cell transfusions. Upper endoscopy did not reveal any source of bleeding. The patient was rapidly prepared with polyethylene glycol and underwent colonoscopy, which revealed active bleeding from the appendiceal orifice (Figure 1). The exact etiology of the appendiceal bleeding could not be ascertained. Hemostasis was achieved with epinephrine (diluted 1:10,000) injections to the periphery of the appendiceal orifice, followed by placement of five hemoclips to effectively close the appendiceal orifice (Figure 2). It was expected that closure of the orifice would provide some tamponade effect and allow for clot formation, since it was not possible to get to the actual lesion inside the appendix. Postcolonoscopy, the patient's hemoglobin and hemodynamics remained stable without any further bleeding. An abdominal CT showed an unusual course of the colon, with the cecum being in the left side of the abdomen (Figure 3) and an irregular thickening of the appendix wall (Figures 3, 4), raising the possibility of an appendiceal mass. On hospital day 4, the patient underwent appendectomy and partial cecectomy. Pathology revealed focal ulceration of the mucosa without malignancy (Figures 5, 6). The remainder of the patient's hospital course was uneventful and he was discharged.

## DISCUSSION

The annual incidence of lower GIB is around 0.03% in the adult population, with a mean age ranging from 63 to 77 years (Bounds & Kelsey, 2007). Lower GIB makes up one third of GIBs, approximately 80% of which are attributed to colorectal origin (Chiang, Tu, Liao, Shieh, & Sung, 2011). Bleeding from the appendiceal orifice is an extremely rare condition (Park, Kwon, Ko, Hong, & Park, 2010). Various etiologies of appendiceal bleeding exist, including benign erosions and ulcers, endometriosis, appendicitis, lymphomas, carcinoids, aortoappendiceal fistulae, and diverticular

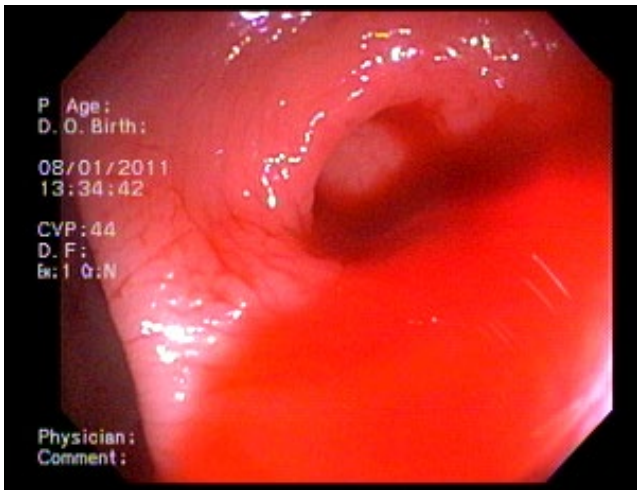


Figure 1 | Active bleeding from appendiceal orifice.

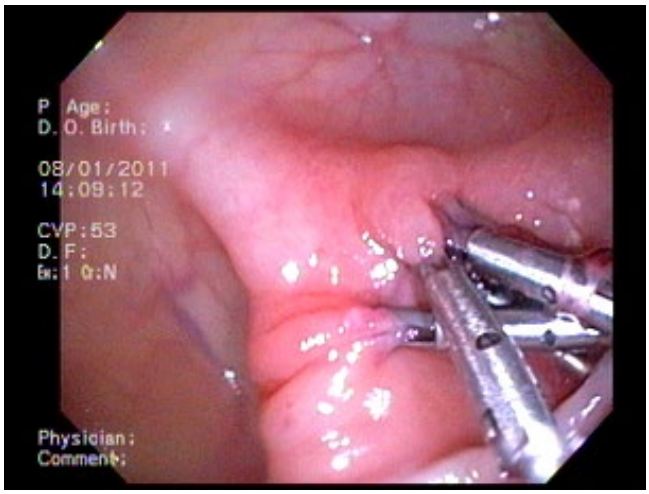


Figure 2 | No bleeding evident after epinephrine injection and appendiceal clipping.

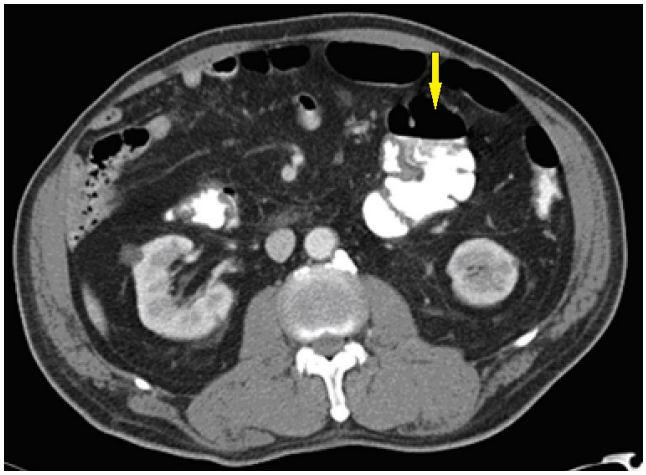

Figure 3 | CT of the abdomen and pelvis shows unusual course of the colon with the cecum in the left side of the abdomen.

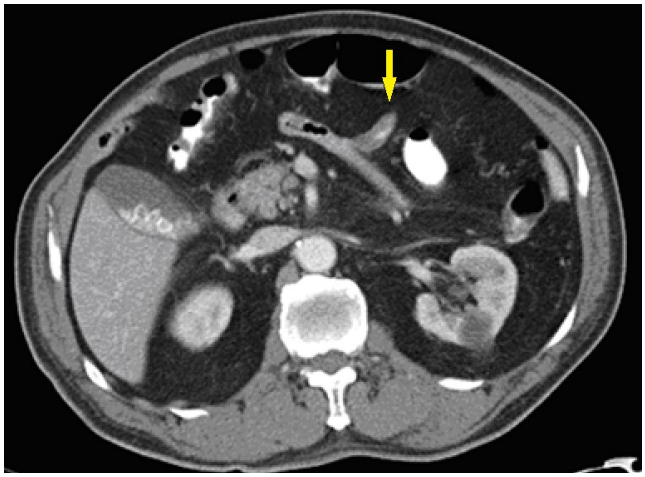

Figure 4 | CT of the abdomen and pelvis shows left-sided appendix with irregular thickening of the appendix wall.

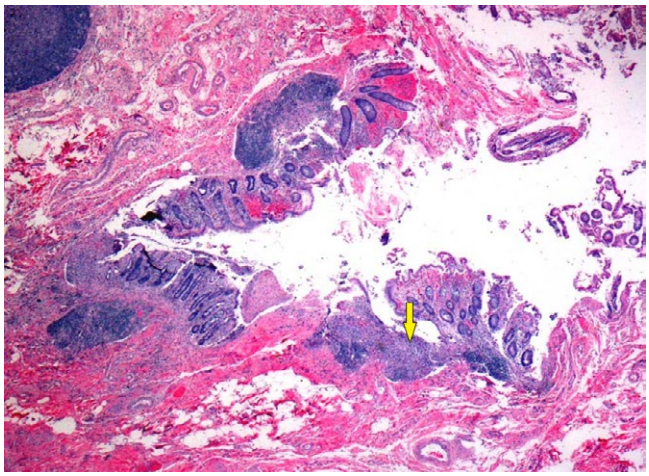

Figure 5 | Histopathology (magnification 40x) revealed appendix with focal ulceration.

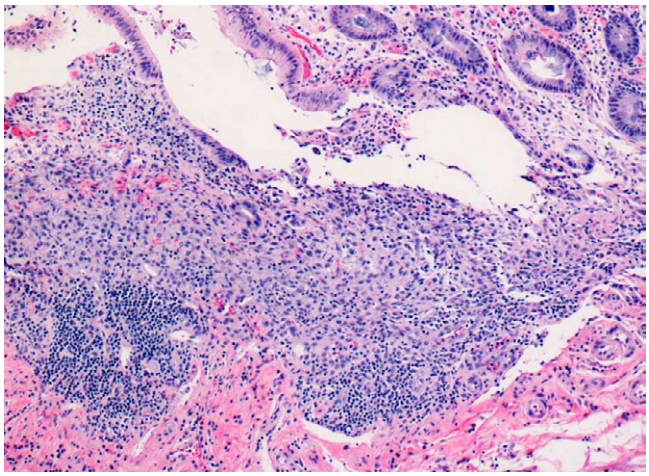

Figure 6 | Magnified histopathology (magnification 400x) of the appendiceal focal ulceration.

disease (Vesa, Hosseini-Carroll, & Manas, 2014). We suspect that our patient's appendiceal bleed originated from an ulcer most likely related to his use of aspirin. Intestinal and colonic ulcers induced by nonsteroidal anti-inflammatory drugs have a tendency to occur in the terminal ileum and proximal colon, where pills are stagnant for an extended period of time. The expected finding on colonoscopy and histology would be nonspecific ulcerations of the small and large bowel, similar to the focal ulceration of the appendiceal mucosa seen in our patient's histopathology specimen (Bounds & Kelsey, 2007). Of interest is the unusual course of the large bowel, with the cecum being found on the left side. This was likely an incidental finding, congenital in etiology, and probably unrelated to the etiology of the bleeding.

Management of any GIB, including from the appendix, is accomplished by various methods such as endoscopic therapy, arterial embolization, or surgery. Baek, Kim, & Kim (2009) conducted an analysis of the medical literature on appendiceal bleeding. All 20 cases reviewed underwent surgical treatment. Surgery is an invasive procedure, and arterial embolization is associated with complications such as rebleeding and ischemia (Chung & Gao, 2011). Endoscopic approaches to treatment, such as endoclips, epinephrine injections, cauterizations, or argon plasma coagulation, are less invasive than surgical approaches; therefore, endoscopic approaches are the preferred primary modality. Endoscopic management of appendiceal bleeding allows for further patient stabilization and, if needed, more-definitive surgical intervention on an elective basis, rather than emergently.

The endoscopic methods of appendiceal clipping used in our case proved effective in achieving hemostasis, and allowed the patient to be stabilized prior to surgery. Furthermore, metal clips can serve as radiographic markers for possible angiographic intervention if colonoscopic attempts fail or if bleeding recurs (Park, Kwon, Ko, Hong, & Park, 2010). In our particular case, the patient underwent definitive surgical intervention during the same admission due to suspicion of a possible mass on imaging. Nevertheless, it would be of interest to further investigate endoscopic appendiceal clipping as a definitive therapy in lieu of surgery and to test the long-term safety and efficacy of this endoscopic procedure. However, considering the rarity of appendiceal bleeding, any such investigation on a large scale is unlikely.

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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.

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# Left-Sided Gallbladder: Uncommon Presentation and Laparoscopic Approach

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Sinistroposition, or left-sided placement of the gallbladder, is a rare congenital anomaly with a prevalence of about 0.3%. These gallbladders, through multiple proposed developmental aberrations, are situated beneath segment III or IV (or both, as in this case) of the liver, and can lead to diagnostic difficulty. We present a case of atypical presentation of acute cholecystitis from a left-sided gallbladder and the modified laparoscopic technique used for its safe removal.

## INTRODUCTION

In an era in which laparoscopic cholecystectomy has become the gold standard for treatment of acute cholecystitis, knowledge of developmental anomalies of the gallbladder and biliary system is essential in order to avoid intraoperative injury to bile ducts (Suhocki & Meyers, 1999).

The embryologic origin of the gallbladder is from the hepatic diverticulum, an out-pouching of the primitive foregut (Ando, 2010). During this early development, a number of malformations may occur: double gallbladder, bilobed (septate) gallbladder, diverticulum of the gallbladder, or gallbladder agenesis (Gross, 1936). Anomalous positions have also been described: intrahepatic gallbladder, left-sided gallbladder, retrodisplacement (at the postero-inferior surface of the liver) of the gallbladder, transverse position of the gallbladder, and floating gallbladder.

This study reports a case of intrahepatic left-sided gallbladder, in an atypical presentation of acute cholecystitis, and describes the modified laparoscopic technique used during cholecystectomy.

## CASE REPORT

A 22-year-old man with a medical history of hypothyroidism and a reducible umbilical hernia presented to the emergency department with a 12-hour history of unrelenting, cramping pain concentrated first in the epigastrium and later migrating to the back, midchest, and entire abdomen. Subjective fever, chills, nausea, and cold sweats accompanied the pain. The patient denied emesis, change in bowel movements, or change in urinary habits.

Physical exam revealed a soft abdomen with tenderness over the epigastrium and left upper quadrant. Laboratory values were within normal limits. A computed tomography (CT) scan was obtained in the face of nonspecific findings, with results suspicious for acute cholecystitis—mildly distended gallbladder with prominent wall, lack of pericholecystic fluid/stranding, and no radio-opaque gallstones (Figure 1). The gallbladder was distended and was seen coursing obliquely toward the left. Porta hepatis and Calot's triangle were both normally located. Abdominal ultrasound revealed a left-sided gallbladder, gallstones, mild wall thickening, distension, and a sonographic Murphy's sign (Figure 2).

The patient underwent laparoscopic cholecystectomy. The initial look revealed the gallbladder oriented obliquely, taking off from the right of the midline and coursing toward the left side. The falciform ligament was situated normally, with the gallbladder running below and across it to the liver segments III and IV. Further dissection at the Calot's triangle revealed that the cystic duct was taking off anterolateral to the common bile duct and the cystic artery was located posterior to the cystic duct, with almost anteriorly oriented perpendicular takeoff from the portal structures. Further distally, the gallbladder was partially intrahepatic, reaching up to the liver margin (Figure 3).

Decompression of the gallbladder allowed us to grasp the distended and inflamed gallbladder. In order to improve access to the gallbladder's unusual location, additional 5-mm ports were added in the left lower quadrant and right lower quadrant (lumbar region). From this vantage point, the cystic duct and artery were both dissected and ligated, and the gallbladder was removed.

## DISCUSSION

Hochstetter first described an anomalous, left-sided gallbladder in 1886, and a multicenter series of laparoscopic cholecystectomies shows a prevalence of 0.3% (Hochstetter, 1886; Idu, Jakimowicz, Iuppa, & Cuschieri, 1996). While about 149 cases of left-sided gallbladder have been reported in the past, only a handful of these cases has been diseased (Dhulkotia, Kumar, Kabra, & Shukla, 2002).

Several theories exist about the etiology of left-sided gallbladder. Cases such as this one show a cystic duct anterolateral to the common bile duct, an anatomically normal configuration. The resulting left-sided gallbladder may have occurred from hepatic diverticulum after normal development, and subsequent migration toward the left lobe instead of rightward (Gross, 1936). This theory would be consistent with our case, as it results in normal orientation of the cystic duct and artery. Another explanation is the com-

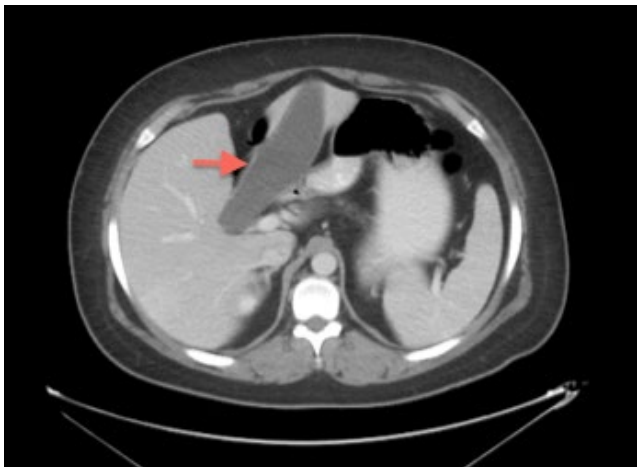

**Figure 1 | CT showing gallbladder (red arrow) traveling obliquely toward the left.**

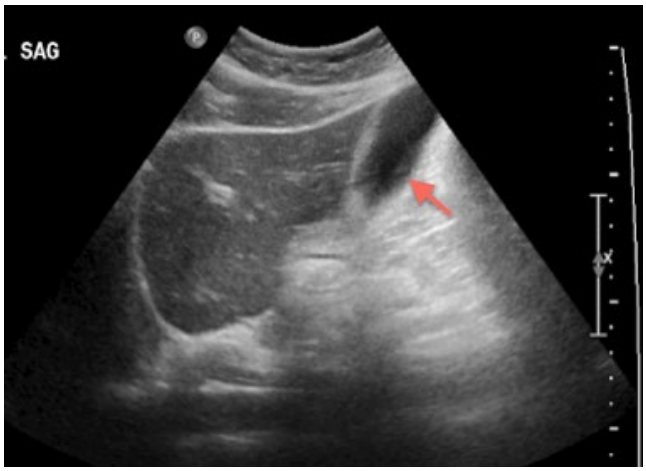


**Figure 2 | Ultrasound study showing gallbladder tip (red arrow) associated with left lobe of liver.**

plete agenesis of the normal gallbladder, in conjunction with the development of a second gallbladder from the left hepatic duct (Gross, 1936). Finally, a Japanese study has found that suspected left-sided gallbladders were in their normal anatomic location, and that the anomalies were actually in right-sided falciform ligaments (Nagai, Kubota, & Kawasaki, 1997).

Several therapeutic implications exist for this anatomic variation, as they are associated with anomalies in the intrahepatic portal vein, cystic duct, and accessory liver (Hsu, Chen, & Huang, 2007; Ikoma, Tamaka, & Hamada, 1992). For example, left-sided gallbladders have been reported with a cystic duct entering the left hepatic duct, making surgery potentially more hazardous (Gross, 1936). Clinically, the presentation of cholecystitis in a left-sided gallbladder (as above, with epigastric and left upper-quadrant pain) may be confused with cardiac or pancreatic pathologies. A laparoscopic approach to cholecystectomy has been successful, with several proposed modifications to surgical technique. One approach used a traditional right-side port placement, with a window created in the falciform ligament to access the left side (Hopper, Ryder, Swarnkar, & Stephenson, 2003). Anterograde dissection—a "dome down" approach via laparoscopy—has also been proposed (dissecting from the fundus), as is traditionally done with open cholecystectomy (Schiffino, Mouro, Levard, & Dubois, 1993). Finally, the placement of left-sided ports, as performed in our case, may provide better access (Zografos, 2009). Additionally, intraoperative cholangiography may aid in the visualization and confirmation of biliary architecture prior to dissection (Corbajo, Martin del Omo, & Blanco, 1999). Open cholecystectomy should always be kept in mind as an option, but with careful use of procedural and imaging techniques as described, a surgeon encountering this diagnosis will have a better chance of avoiding open surgery and common bile-duct injury.

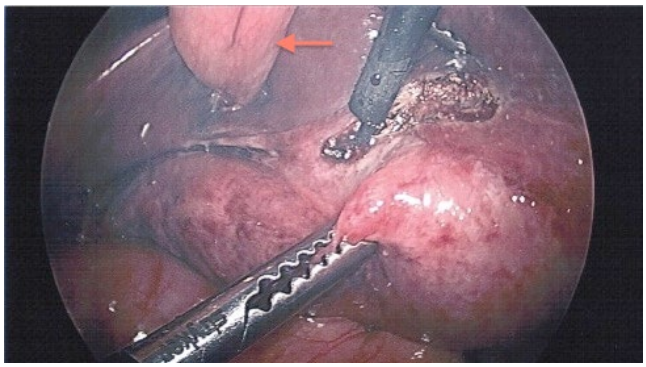

**Figure 3 | Dissection of gallbladder with intrahepatic portion inside left lobe; falciform ligament (red arrow).**

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**Author Contributions:** QKN conceived the study and prepared the manuscript. AJ provided guidance and editing of the manuscript.

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

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# Coffee Consumption and Cardiovascular Disease Risk: What Should We Tell Our Patients?

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The association between coffee and the risk of cardiovascular disease has been studied over the past 20 years. Given the complexity of conducting large, randomized, controlled trials to prove causality, conclusions are based on case reports, retrospective studies, and small physiologic trials. Surveys determine that most physicians advise discontinuing or reducing consumption of caffeine in patients with known heart disease, yet this recommendation lacks strong supporting evidence. The following is a short review of the effects of coffee and caffeine on the cardiovascular system that aims to provide objective advice to physicians and patients based on the published literature.

*Hypothetical Case: A 40-year-old female with no significant past medical history presents to your primary care clinic for a routine checkup. She complains of intermittent palpitations and believes that she has a life-threatening cardiac condition because her brother died of a heart attack at a young age. After obtaining a detailed history, you find that she has been under a lot of stress and has been consuming six to seven cups of coffee per day for the past several weeks. Her exam is benign and her electrocardiogram shows nonspecific repolarization abnormalities. Your initial impression is that the patient is suffering from anxiety and you recommend that no further cardiac testing is necessary. After discussing this with your patient you are asked: "Doctor, should I stop drinking coffee? What can caffeine do to my heart?" How would you approach these questions?*

## INTRODUCTION

The association between coffee and the risk of cardiovascular (CV) disease, particularly arrhythmias, has been a topic of research for the past 20 years. However, the conclusions of the published studies have been diverse. Even though caffeine is widely consumed, to date there have been no randomized, controlled trials with adequate statistical power analyzing the direct relationship between caffeine intake and CV risk factors or adverse events. It is important to note that caffeine has been the primary focus of most coffee-consumption studies (O'Keefe et al., 2013), yet it is merely one of hundreds of compounds present in coffee. Our limited knowledge of the relationship between caffeine intake and adverse CV events is based on case reports, retrospective studies, and small physiologic trials with only short-term follow-up that cannot be generalized to all populations. Surveys conclude that most physicians recommend that patients with known heart disease avoid or reduce their caffeine intake, yet strong evidence to support this advice is lacking (Hage & Iskandrian, 2012; Pelchovitz & Goldberger, 2011).

## THE BASICS

Caffeine is a methylxanthine alkaloid derivative (Corti et al., 2002; Frost & Vestergaard, 2005; Glatter, Myers, & Chiamvimonvat, 2012; Hage & Iskandrian, 2012; Mattioli, Farinetti, Miloro, Pedrazzi, & Mattioli, 2011; O'Keefe et al., 2013; Pelchovitz & Goldberger, 2011) present in coffee, chocolate, certain teas, sodas, and some commonly used over-the-counter drugs. In 150 ml of coffee, for example, there are approximately 80 to 100 mg of caffeine (Pelchovitz & Goldberger, 2011). According to the Food and Drug Administration, intake of up to 400 mg of caffeine per day is considered safe (U.S. Food and Drug Administration, 2013). At low or moderate doses (less than 100 mg, or 100–200 mg, respectively), caffeine acts as a nonspecific competitive antagonist of adenosine receptors, inhibits the phosphodiesterase enzyme, and increases cytosolic calcium concentrations, therefore triggering or enhancing cardiac conduction and activity (Hage & Iskandrian, 2012; Kinugawa, Kurita, Nohara, & Smith, 2011). According to laboratory data, caffeine also acts as a sympathomimetic by stimulating the release of catecholamines, which results in vasoconstriction (Frost & Vestergaard, 2005; Mostofsky, Rice, Levitan, & Mittleman, 2012). Immediately after consumption, caffeine affects certain chemoreceptors in the gastrointestinal tract, indirectly causing increased heart rate, cardiac output, and blood pressure to enhance flow to the splanchnic vasculature (Pelchovitz & Goldberger, 2011).

## THE PROS AND CONS

Many studies have revealed undesirable effects of caffeine on the CV system, namely the development of arrhythmias, hypertension, and even heart failure (Birkett & Logan, 1988; Frisoli, Schmieder, Grodzicki, & Messerli, 2011; Mattioli et al., 2011). An increase in systolic blood pressure several minutes to hours after intravenous administration has been demonstrated in animal models in the lab (Bohn, Ward, Hodgson, & Croft, 2012; Corti et al., 2002; Frisoli et al., 2011; McMullen, Whitehouse, Shine, Whitton, & Towell, 2011). Additionally, exacerbation of atrial arrhythmias has been observed in humans after oral consumption (Kinugawa et al., 2011; Parasramka & Dufresne, 2012; Pelchovitz &

| Table 1 \| Effects of Coffee on Cardiovascular Health | |
|---|---|
| Blood Pressure | Transient elevation acutely in nonhabitual drinkers; no effect (tolerance) with regular intake |
| Insulin Sensitivity | Increase in adiponectin levels; decrease in insulin resistance from upregulated IGF-1 signaling |
| Serum Lipids | Increase in total and LDL cholesterol (with boiled coffee, not filtered) |
| HS CRP | Decrease |
| Arrythmias | No association between consumption and incidence of supraventricular arrythmias, or frequency or severity of ventricular arrythmias |
| Congestive Heart Failure | Decrease in risk with four cups per day; increase in risk with fewer than or more than four cups per day (U-shaped curve, not statistically significant) |
| Coronary Heart Disease | Decrease in risk with moderate consumption (one to two cups per day) |
| Mortality | Decrease in risk of cardiovascular mortality in patients without preexisting cardiovascular disease (dose-response protective effects) |

Goldberger, 2011). Based on the observations made by Kinugawa et al., the effect of caffeine on atrial rhythms is more pronounced when high doses are administered to subjects who might be caffeine sensitive (Kinugawa et al., 2011). It is important to note, however, that these hypotheses are based on limited observations, that the acute effects of caffeine administration tend to resolve within several hours, and that tolerance to caffeine's effects readily develops when caffeine is regularly consumed. Because of these observations, the long-term effects of caffeine consumption on blood pressure and arrhythmias are not considered clinically significant; however, prospective randomized studies to evaluate the longitudinal effects of caffeine have not been conducted (Corti et al., 2002; McMullen et al., 2011; Pelchovitz & Goldberger, 2011). A random survey in 1988 of more than 2,000 patients concluded that there was no statistically significant evidence that habitual caffeine intake increased the risk of hypertension (Birkett & Logan, 1988).

In a canine model, the degree and severity of arrhythmias secondary to caffeine administration were found to be dose-related. In small clinical studies, moderate coffee consumption was associated with atrial fibrillation persistence, particularly in hypertensive patients (Kinugawa et al., 2011; Mattioli et al., 2011). After analyzing a case of atrial tachycardia exacerbated by caffeine and after reviewing other caffeine-related arrhythmia cases, Kinugawa concluded that in certain patients, moderate caffeine consumption can produce QRS interval prolongation and shorten effective refractory period of the right atrium, the atrio-ventricular node, and the right ventricle, which may be associated with significant atrial and ventricular arrhythmias (Kinugawa et al., 2011). However, case reports cannot always demonstrate causality, and the possibility that these patients might be particularly sensitive to caffeine due to baseline conduction abnormalities cannot be ruled out.

Table 1 summarizes the effects of coffee consumption on cardiovascular health, which are well described by O'Keefe et al. (2013). Klatsky, Hasan, Armstrong, Udaltsova, and Morton (2011) found that moderate caffeine intake was inversely related to the risk of hospitalization due to arrhythmias, suggesting that it is highly unlikely that caffeine ingestion increases arrhythmia risk. The consumption of 4 cups of coffee per day had a moderate but statistically significant inverse relationship with heart-failure incidence, yet, as the consumption per day increased, the association had no statistical significance (the so-called J-curve relationship) (Mostofsky et al., 2012). A cohort from the Danish Diet, Cancer, and Health Study did not discover an association between the amount of caffeine consumed per day and the risk of atrial fibrillation or flutter (Frost & Vestergaard, 2005). This study had the strength of a large sample size, given the high coffee consumption and prevalence of atrial fibrillation in Denmark. It is important to note that these studies are observational and subject to behavioral bias.

Most epidemiological data related to caffeine consumers suggest that moderate coffee intake is not associated with CV disease and might even have protective effects (Hage & Iskandrian, 2012). Studies have suggested that caffeine metabolites may even have positive effects on endothelial function, glucose metabolism, cholesterol transport, oxidative stress, and platelet function, among other processes (Bohn et al., 2012; Mattioli et al., 2011). Caffeine may reduce atherosclerosis via several active compounds that function as potent antioxidants, which can reduce reactive nitrogen species, protect against apoptosis, and even reduce oxygen consumption in vascular smooth muscle (Mercer, Gray, Figg, Kumar, & Bennett, 2012).

**THE BOTTOM LINE . . .**

The available literature suggests that caffeine consumption is generally safe, but reports of its indirect effects on the cardiovascular system must not be completely disregarded. These findings should prompt us to educate patients about the possible acute effects of moderate to high caffeine doses in nonhabitual consumers and advise patients with

preexisting cardiovascular disease to consume with caution until the medical community has a clear understanding of caffeine's direct relationship with CV disease.

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# Psychiatric Underpinnings of Chronic Diabetic Neuropathic Pain

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There is increasing evidence that psychosocial factors may be involved in the pathophysiology of chronic diabetic neuropathic pain. Individuals with diabetic polyneuropathy exhibit significantly higher rates of axis I psychiatric disorders, and worsening neuropathic symptoms correlate with worsened psychiatric illness. This association exists even when social-support and quality-of-life measures are controlled. Aberrant supraspinal structures and neuronal networks in diabetic neuropathy mimic those found in other psychiatric illnesses. Response to standard medications and therapeutic approaches remains unsatisfactory, and antidepressants continue to serve as first-line treatment for diabetic neuropathy. The exact interplay between neuropathic pain and psychiatric illness remains unclear and may have a common pathophysiological focus. This area of study needs to be revisited and psychological interventions must be explored as possible treatment options for diabetic neuropathy.

The International Diabetes Foundation estimates that 382 million people worldwide have diabetes, and projects that this number will rise to 592 million people by the year 2035 (*IDF Diabetes Atlas*, 2013). In the United States alone, nearly 26 million people (8.3% of the population) are affected by diabetes, with 1.9 million new cases diagnosed each year. Prevalence of diabetic neuropathy varies by population and socioeconomic status, but a recent large-scale, community-based study from England found that almost 50% of diabetic patients showed signs of clinical neuropathy (defined as the inability to detect pinprick sensation, vibration, differences in temperature, and Achilles reflex). Twenty-one percent of these patients complained of painful neuropathic symptoms, compared with 26% of patients without clinical neuropathy who complained of painful neuropathic symptoms (Abbott, Malik, van Ross, Kulkarni, & Boulton, 2011).

Neuropathic syndromes are classified as acute, if they last less than three months, or chronic, if they last longer than three months (Bouhassira, Lantéri-Minet, Attal, Laurent, & Touboul, 2008). Chronic diabetic neuropathic pain syndromes tend to be more debilitating than their acute counterparts, and present with symptoms ranging from mild dysesthesias to severe, unremitting pain. The pain itself may be completely stimulus-independent or evoked only with mechanical, thermal, or chemical stimulation (Jose, Bhansali, Hota, & Pandhi, 2007; Morello, Leckband, Stoner, Moorhouse, & Sahagian, 1999; Vinik, Park, Stansberry, & Pittenger, 2000).

The exact pathophysiology of chronic neuropathic pain in diabetes has not yet been identified and is believed to be multifactorial in nature. Several mechanisms have been posited over the years, and both the peripheral and central nervous system have been implicated. Hyperglycemia clearly plays a role, and even slight perturbations in blood-glucose levels, as seen in impaired glucose tolerance, can precipitate nerve damage and dysfunction (Smith & Singleton, 2008). Hyperglycemia increases nonenzymatic glycation of structural proteins and polyol accumulation, alters protein kinase C activity, decreases nitric oxide, and increases poly ADP-ribose polymerase activation, causing oxidative stress and resultant nerve damage and impaired nerve repair (Tavakoli, Mojaddidi, Fadavi, & Malik, 2008; Tomlinson, 1999). There are also microangiopathic changes that parallel and often precede apparent nerve-fiber injury (Dyck & Giannini, 1996; Malik et al., 2005; Thrainsdottir et al., 2003).

Studies conducted on sural nerve biopsies obtained from diabetic patients with clinically confirmed neuropathies demonstrate progressive length-dependent nerve fiber loss (Yagihashi, 1995). Ongoing nerve damage and impaired repair lead to peripheral hyperexcitability with lowered activation thresholds and spontaneous neuronal discharge (Krishnan & Kiernan, 2005). This activity is perceived by patients as spontaneous pain and dysesthesia, or as an exaggerated response to noxious or otherwise benign stimuli. With increasing neuronal loss, positive symptoms eventually give way to negative symptoms such as sensory loss. In a subset of patients, however, positive symptoms fail to resolve, which hints at a role for centrally mediated or psychiatric mechanisms in the abnormal sensations.

There is increasing evidence that psychosocial factors may be involved in the pathophysiology of chronic diabetic neuropathic pain (Calcutt, 2002). Individuals with diabetic polyneuropathy exhibit significantly higher rates of axis I psychiatric disorders—especially anxiety disorders and major depressive disorders—compared with diabetic patients without neuropathy. Moreover, the severity of the depressive symptoms correlates positively and significantly with the severity of the neuropathic symptoms (Moreira et al., 2007). However, the chronological order and interplay between neuropathic pain and psychiatric illness still remain unclear. There is ample evidence that chronic painful neuropathy can lead to physical impairments and impose functional limitations that drastically lower the level of patients' effective well-being (Benbow, Wallymahmed, & MacFarlane, 1998; Rijken et al., 1998). Patients complain of

disturbances in mood, sleep, work, and activities of daily living, all of which can lead to increases in depression, anxiety, and anger (Robinson, Yateman, Protopapa, & Bush, 1990; Watkins, 1984; Zelman, Brandenburg, & Gore, 2006). When beset by unremitting pain, patients may lose their coping mechanisms and become overly sensitive to and preoccupied with their neuropathic symptoms (Feldman, Downey, & Schaffer-Neitz, 1999). Neuropathy has been found to be significantly associated with depression, even when the analyses control for social-support and quality-of-life measurements (Yoshida, Hirai, Suzuki, Awata, & Oka, 2009). Stress, anxiety, and depression are also highly associated with the development of diabetes. Large prospective epidemiological studies and meta-analyses suggest a bidirectionality and, therefore, a common pathogenesis underlying diabetes and psychiatric disorders (Engum, 2007; Knol et al., 2006; Mezuk, Eaton, Albrecht, & Golden, 2008; Pan et al., 2010; Pouwer, Kupper, & Adriaanse, 2010).

A basis for mood disorders and preoccupation with neuropathic symptoms in diabetic patients may be found in studies of neuronal networks and connectivity. Cauda et al. (2009) studied a group of eight diabetics suffering from painful neuropathy and compared them with healthy controls using functional magnetic resonance imaging. They found that neuropathic patients had reduced default mode network (DMN) connectivity while showing increased connectivity among several frontal areas, insulae, and thalami (Cauda et al., 2009). The DMN refers to a network of brain regions composed of the medial prefrontal cortex, the posterior cingulate cortex/precuneus, and the lateral posterior cortices. This network is known to be most active during states of wakeful rest, and least active during task-related cognitive processes (Fox et al., 2005). The DMN has been found to be significantly affected in Alzheimer's disease, autism, schizophrenia, post-traumatic stress disorder, and depression (Andreescu et al., 2013; Buckner, Andrews-Hanna, & Schacter, 2008; Cisler, Scott Steele, Smitherman, Lenow, & Kilts, 2013). Since the DMN underlies self-reflection and modulation of emotion, reduced activity in patients with chronic neuropathy suggests that they have a decreased ability to regulate pain and emotions while spending more cognitive resources in the catastrophization of pain.

Several supraspinal structural abnormalities have also been implicated in painful diabetic neuropathy and involve the thalamus in particular. Selvarajah et al. (2008) found that patients with diabetic peripheral neuropathy had significantly lower ratios of thalamic N-acetyl aspartate (NAA) to creatine and of NAA to choline compared with controls. Sorensen, Siddall, Trenell, and Yue (2008) also studied NAA levels in the thalami of diabetic patients and found that patients with chronic pain had markedly reduced levels of the compound compared with diabetic patients without pain. NAA is a free amino acid in the brain and is commonly used as an internal standard for neuronal integrity and activity. It is often used in the study of psychiatric conditions and has been found to be significantly reduced in the thalami of patients suffering from depression (Huang et al., 2010), schizophrenia (Kraguljac et al., 2012; Tandon et al., 2013), cognitive impairment (Salem et al., 2008), restless legs syndrome, essential tremors (Kendi, Tan, Kendi, Erdal, & Tellioglu, 2005), and substance abuse (Li, Wang, Pankiewicz, & Stein, 1999). The underlying mechanism of thalamic dysfunction in these conditions is currently unclear, especially in light of the thalamus's innumerable functions. However, the thalamus's role in movement, pain perception and modulation, and identification of emotional information, and its generation of affective states, are increasingly being recognized. It is not unlikely, therefore, that thalamic dysfunction underlies the psychiatric component of the pathophysiology of diabetic chronic neuropathic pain, as either a primary or a secondary process.

Neuropathic pain responds poorly to standard therapeutic approaches, and a large percentage of patients remains refractory to the therapies available despite an ever-increasing catalogue of drugs (Vinik et al., 2000). More than half of the patients do not respond to treatment, and those who do respond report only a 30% to 40% reduction in pain (Dworkin et al., 2010; O'Connor, 2009; Turk, 2002). There is little agreement about the optimal treatment regimen for neuropathic pain, though many different guidelines exist (Attal et al., 2010; Bril et al., 2011; Dworkin et al., 2007; Moulin et al., 2007). There is some agreement about which classes of medicine seem to work better, with first-line treatments including antidepressants (tricyclic antidepressants, selective norepinephrine reuptake inhibitors), calcium channel alpha 2-delta ligands (pregabalin), and topical lidocaine. The effectiveness of antidepressants in the treatment of neuropathic pain lends further support to the notion that a psychiatric etiology plays at least some role in the condition's modulation. Second-line medications consist of opioid analgesics and tramadol, while third-line treatments include such medications as capsaicin, mexiletine, and N-methyl-d-aspartate receptor antagonists (O'Connor & Dworkin, 2009).

Psychological interventions for neuropathic pain have received little attention, but they are supported by considerable data and empirical evidence of benefit in the management of heterogeneous chronic pain conditions (Brunelli & Gorson, 2004; Flor, Fydrich, & Turk, 1992). These psychological interventions focus on the emotional distress and maladaptive behaviors that accompany and exacerbate pain, and teach patients to adapt and manage their lives in the face of unrelenting, chronic pain (Turk, Audette, Levy, Mackey, & Stanos, 2010). Some interventions suggested for treatment of neuropathic pain include biofeedback, hypnosis, social support, operant behavioral interventions, and cognitive behavioral interventions (Haythornthwaite & Benrud-Larson, 2000, 2001; Turk et al., 2010). Operant conditioning refers to a treatment approach wherein reinforcement is used to promote positive behaviors while discouraging maladaptive behaviors. In the context of diabetic neuropathy, this approach discourages healthcare professionals from positively reinforcing ostensible pain-associated behaviors such as limping and griping about the pain. Cognitive behavioral interventions differ from operant conditioning in that they additionally target internal cognitive reasoning in patients, helping them develop coping mecha-

nisms and, as a result, a sense of control over their pain. Biofeedback employs quantifiable, physiological metrics (such as blood pressure, heart rate, and sweat-gland activity) and makes them available to patients in real time to bring unconscious thoughts and behaviors that exacerbate pain under conscious control (Turk et al., 2010).

Although the role of psychological modalities in the treatment of chronic neuropathic pain has historically been limited, there is increasing evidence that pain reduction using these methods rivals that observed with more-traditional pharmacological treatments (Otis et al., 2013; Turk et al., 2010). As individual treatments have met with very limited success, psychological modalities provide a promising complement to medical therapy in achieving better outcomes for patients.

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# More Than Skin Deep: Genetics, Clinical Manifestations, and Diagnosis of Albinism

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Although albinism may be considered a simple diagnosis, its clinical manifestations, which include hypopigmentation of the skin, hair, and eyes and ocular abnormalities such as nystagmus and reduced visual acuity, are often subtle and initially missed. In oculocutaneous albinism, there is wide phenotypic variability, which correlates with specific mutations in genes with roles in melanin biosynthesis. Additionally, syndromic forms of albinism such as Hermansky-Pudlak syndrome, Chediak-Higashi syndrome, and Griscelli syndrome are associated with serious complications such as bleeding abnormalities, lysosomal storage defects, immunodeficient states, and progressive neurologic defects, which all can result in mortality. It is critical to confirm a suspicion of albinism and perform an appropriate workup involving molecular testing in order to establish a diagnosis. Given the various subtypes of oculocutaneous albinism and the life-threatening complications in syndromic forms of albinism, a diagnosis permits proper genetic counseling and timely implementation of necessary screenings and treatments. Recommendations regarding sun exposure and treatment of ocular abnormalities are imperative in oculocutaneous albinism, and preventive therapies should be implemented in syndromic forms. With knowledge of the differential in conjunction with the execution of simple diagnostic tests, many of these complications can be predicted and consequently ameliorated or prevented.

## INTRODUCTION

Albinism is an inherited condition affecting approximately one in 17,000 persons and is characterized by absent or reduced pigmentation in the skin, hair, and eyes (oculocutaneous albinism [OCA]), or only the eyes (ocular albinism) (C. J. Witkop, 1979). There are various associated manifestations, including systemic pathologies in syndromic albinism. Hypopigmentation may be subtle and missed in neonates and become apparent only with age and sun exposure, and ocular abnormalities and systemic complications may not develop for years, leading to delayed diagnoses and treatment (Torres-Serrant, Ramirez, Cadilla, Ramos-Valencia, & Santiago-Borrero, 2010). Therefore, it is imperative to confirm a diagnosis of albinism and to be aware of the systemic symptoms of associated syndromes. Although most persons with albinism have a presentation limited to OCA, in the face of additional symptoms, one must consider syndromes such as Hermansky-Pudlak syndrome (HPS), Chediak-Higashi syndrome (CHS), and Griscelli syndrome (GS).

## PATHOGENESIS OF PIGMENTATION

Melanocytes are derived from neural crest precursors known as melanoblasts, which are guided by signaling pathways toward destinations including the basal epithelium of the epidermis, the hair bulbs of the skin, and the uveal tract of the eye (Dessinioti, Stratigos, Rigopoulos, & Katsambas, 2009). Once in target sites, melanoblasts differentiate into functional melanocytes by synthesizing melanin within lysosome-like organelles called melanosomes, within which tyrosine is converted to melanin. Melanosomes are then transferred via melanocytic dendrites to surrounding keratinocytes (Dessinioti et al., 2009).

Melanin is derived from tyrosine and its synthesis is primarily regulated by tyrosinase, *P* gene, tyrosinase-related protein 1 (TYRP1), and membrane-associated transporter protein (MATP), which are each mutated in the OCA subtypes (Figure 1). Tyrosinase catalyzes the hydroxylation of tyrosine to dopaquinone in the bottleneck step of melanin synthesis. Diversion to two pathways then occurs, with one synthesizing the eumelanin that composes brown and black pigments, and the other synthesizing pheomelanin, which is responsible for blonde and reddish pigments (Levin & Stroh, 2011). Pigmentation is therefore affected by several factors: host cell presence, melanosome formation, and the quantity of melanin within melanosomes. Of note: while OCA is associated with defects in melanin production, syndromic albinism is attributed to defective formation and transport of melanosomes (Scheinfeld, 2003).

## OCULOCUTANEOUS ALBINISM

OCA is a group of autosomal recessive (AR) disorders caused by absent or deficient melanin biosynthesis, manifesting as generalized hypopigmentation of the hair, skin, and eyes and ocular abnormalities. It is attributed to defects in four genes (*OCA1–4*), with much of the phenotypic variation attributed to compound heterozygosity (Gronskov, Ek, & Brondum-Nielsen, 2007).

The degree of skin and hair pigmentation varies according to the type of OCA. Iris hypopigmentation is associated with reduced visual acuity, nystagmus, photophobia, foveal hypoplasia, strabismus, refractive error, color-vision impairment, and amblyopia. These defects may be related to abnormal misrouting of the optic nerves (Creel, Summers, & King, 1990). Visual evoked potentials reveal characteristic patterns representing abnormal decussation and can confirm OCA (Moss, 2000). Nystagmus, which is typically the most clinically apparent ocular abnormality, may not appear

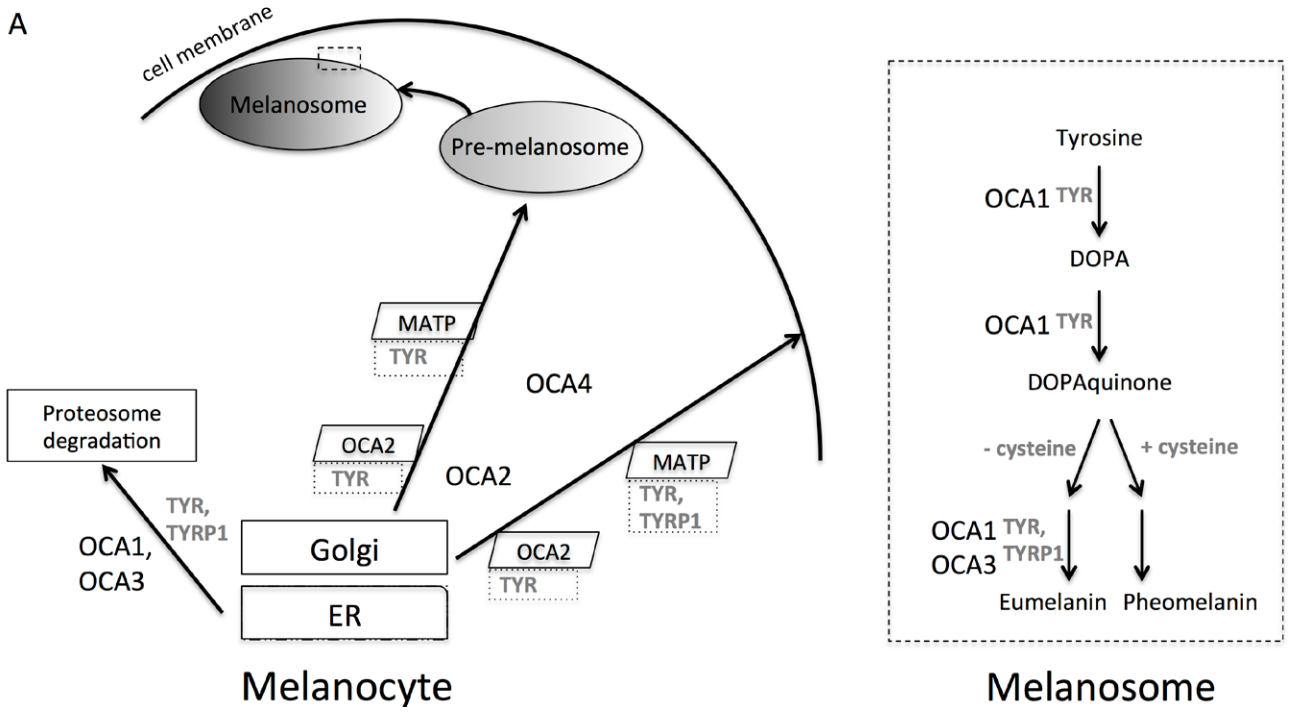


**Figure 1 | Melanosome formation and melanin biosynthesis in the melanocyte and melanosome, respectively.** (A) Melanosome biogenesis within the melanocyte and sorting of melanosome proteins TYR and TYRP1 from the endoplasmic reticulum and golgi to the developing melanosome via OCA2 and MATP proteins. Minor TYR or TYRP1 mutations lead to proteasome degradation, causing disease. Mutations in TYR, OCA2, TYRP1, and MATP cause OCA1, OCA2, OCA3, and OCA4, respectively. (B) Melanin biosynthesis may be disrupted by TYR or TYRP1 mutations, causing OCA1 and OCA3, respectively. Adapted from Grosnkov, Ek, & Brondum-Nielsen, 2007. TYR: tyrosinase, TYRP1: tyrosinase-related protein 1.

until the patient is 2 to 3 months old. Parents may initially think that the infant is unable to fixate on targets, as the nystagmus manifests in a large-amplitude and low-frequency pattern (Levin & Stroh, 2011; Moss, 2000). With age, the nystagmus becomes pendular, followed by development of the typical jerk nystagmus (Levin & Stroh, 2011).

Type 1 OCA (OCA1) is itself divided into four subtypes, all bearing mutations in the tyrosinase gene (*TYR*), which is mapped to chromosome 11q14-2. Phenotypic manifestations of each subtype are directly related to the type of *TYR* mutation.

Type 1A OCA is the most clinically severe, as tyrosinase activity is absent secondary to a null mutation in each copy of *TYR* (Giebel, Musarella, & Spritz, 1991). Individuals with this mutation are born with white skin and hair and light-blue to pink irises; they later manifest nystagmus, poor visual acuity, and prominent photophobia. Their skin cannot tan and can develop only amelanotic nevi.

Type 1B OCA is caused by a point mutation in *TYR* that changes the conformation of tyrosinase or causes new splicing sites (Matsunaga et al., 1999). Decreased tyrosinase activity permits some melanin accumulation over time. Although at birth the phenotype may be indistinguishable from that of type 1A, pigment may rapidly accumulate. Hair may grow with a white-tipped pattern and appear blonde or light brown, due to preferential shunting to the pheomelanin pathway, and iris color may change from blue to green or brown (Giebel et al., 1991; Gronskov et al., 2007). As in type 1A, vision is moderately to severely reduced, with prominent nystagmus developing soon after birth.

Type 1MP OCA, the "minimal pigment" form of OCA1, has decreased tyrosinase activity, permitting some pigment, with blonde hair color and pigmented nevi developing. Type 1 TS OCA is the "temperature-sensitive" form resulting from a *TYR* missense mutation that produces tyrosinase with activity that varies according to temperature (Giebel et al., 1991). While its initial presentation may also be indistinguishable from that of type 1A, during puberty tyrosinase function becomes normal in the cooler areas of the body, producing dark hair on the arms, legs, and chest; white hair remains in the warmer areas, including the axilla, pubic region, and scalp (Levin & Stroh, 2011).

The molecular genetic defect in Type 2 OCA (OCA2) is in the *P* gene, now known as *OCA2*, mapped to 15q11.2–11.3 (Ramsay et al., 1992). It encodes a melanosomal membrane protein that regulates the influx of proteins such as TYR and TYRP1 (Levin & Stroh, 2011). Manifesting with some pigment production, skin and hair color range from white to fair and yellow to black, and eyes are typically

light blue with improved ocular function compared to the 1A phenotype. Newborns usually have pigmented hair and irises, with typical nevi and ephileds (Gronskov et al., 2007). Clinically, OCA2 is most comparable to types 1B and 1MP and it is the most prevalent form worldwide, affecting about one in 10,000 African Americans (Oetting & King, 1999). Approximately one in 100 patients with Prader-Willi or Angelman syndromes also manifest OCA2, as *OCA2* is located in the region of chromosome 15 between the genes responsible for these syndromes (Lee et al., 1994).

Type 3 OCA (OCA3) is caused by mutations in *TYRP1,* which encodes an enzyme that catalyzes eumelanin formation and stabilizes TYR (Toyofuku et al., 2001). As this type presents with a minimally hypopigmented phenotype, it is almost exclusively described in South African blacks, although it has recently been described in other populations (Tomita & Suzuki, 2004; K. H. Zhang et al., 2011). Mutations in *TYRP1* are responsible for brown or rufous albinism; brown albinism presents with light-brown skin pigment, beige to light-brown hair, and blue-green to brown irises, while the rufous phenotype is characterized by a red-bronze skin with nevi, ginger-red hair, and blue or brown irises (Kromberg et al., 1990). In one Caucasian patient with *TYRP1* mutation, hair was yellow-gold with orange highlights. Otherwise, the phenotype was indistinguishable from types 1B and OCA2 (Rooryck, Roudaut, Robine, Musebeck, & Arveiler, 2006).

Type 4 OCA is caused by mutations in *MATP*, which has suggested roles in protein transport and melanosome function. The clinical phenotype is similar to type 1A OCA but is most common in Japan (Tomita & Suzuki, 2004).

There are increasing numbers of OCA subtypes due to digenic inheritance. For example, a mutation in the microphthalmia-associated transcription factor (*MITF*) gene combined with a *TYR* mutation produces ocular albinism with deafness, which may be attributed to melanin's role within the stria vasculosa of the ear (Chiang, Spector, & McGregor, 2009). Due to clinical overlap among the various types of OCA and increasing subtypes, molecular diagnosis permits proper counseling, implementation of appropriate precautions and interventions, and differentiation from subtypes with defined morbidities and mortality.

## SYNDROMIC OCULOCUTANEOUS ALBINISM

### Hermansky-Pudlak Syndrome

HPS is a rare AR disease, affecting one in 500,000 to 1,000,000 persons, but it is quite common in Switzerland and Puerto Rico, affecting one in 1,800 northwestern Puerto Ricans (C. J. Witkop et al., 1990). This syndrome is attributed to at least nine distinct genetic defects causing subtypes HPS1–9 and is characterized by OCA, bleeding abnormalities, and lysosomal ceroid storage defects in some subtypes (Krisp, Hoffman, Happle, Konig, & Freyschmidt-Paul, 2001). HPS gene products were identified as subunits of at least three multiprotein complexes named biogenesis of lysosome-related organelle complex (BLOC) -1, -2, and -3, with roles in intracellular protein trafficking and newly defined interactions with the actin cytoskeleton (Dell'Angelica, 2004; Ryder et al., 2013). The symptoms are attributed to abnormalities in the function and formation of intracellular vesicles, such as melanosomes in melanocytes, dense bodies in platelets, and lytic granules in T cells, neutrophils, and lung type II epithelial cells (Dessinioti et al., 2009; Wei, 2006). Albinism results from protein mistrafficking that disables melanosome production, forming macromelanosomes that can be observed on skin biopsy (Levin & Stroh, 2011). The platelet dysfunction is attributed to deficiency of dense bodies, which normally trigger the secondary aggregation response. This leads to a prolonged bleeding time with normal platelet counts and normal coagulation factor activity (Torres-Serrant et al., 2010). The lysosomal storage defect is demonstrated by a yellow, autofluorescent, amorphous lipid-protein complex, called ceroid lipofuscin, in urinary sediment and parenchymal cells; it predisposes patients to the development of granulomatous colitis, renal failure, cardiomyopathy, and pulmonary fibrosis.

The *HPS1* gene, located on chromosome 10q23.1–q23.3, encodes a transmembrane protein that regulates protein traffic targeted to melanosomes. It is the most frequently presenting HPS mutation and is phenotypically very similar to HPS4 (Wei, 2006). HPS1 and HPS4 are the most severely affected of the subtypes, with prominent OCA, prolonged bleeding, complications from granulomatous colitis, and early death from pulmonary fibrosis. The *HPS4* gene is mapped on chromosome 22q11.2–q12.2, and intracellular HPS1 and HPS4 proteins associate together in BLOC-3 (Wei, 2006).

HPS2 can be clinically distinguished, as it causes immunodeficiency and manifests with congenital neutropenia and recurrent respiratory illness (Jung et al., 2006). It is attributed to mutations in the *AP3B1* gene, which encodes the Beta3A subunit of the heterotetrameric adaptor protein complex known as adaptor protein-3 (AP-3), which acts in mediating cargo-protein selection in transport vesicles and in sorting proteins to lysosomes (Dell'Angelica, 2004; Wei, 2006). The immunodeficiency is caused by a deficient AP3-dependent antigen presentation pathway and loss of microtubule-mediated movement of enlarged lytic granules in cytotoxic T-lymphocytes, among other innate immunity defects (Fontana et al., 2006; Sugita et al., 2002).

The *HPS3* gene is mapped to chromosome 3q24 and contains sorting signals for targeting to vesicles (Anikster et al., 2001). It is commonly associated with central Puerto Rican or Ashkenazi Jewish ancestry and is clinically similar to HPS5 and HPS6, presenting with very mild skin hypopigmentation, ocular albinism, visual acuity of approximately 20/100 or better, and mild bruising, without colitis or pulmonary fibrosis. The defective proteins in HPS3, HPS5, and HPS 6 interact with one another in BLOC-2 and regulate organelle biosynthesis (Huizing et al., 2009; Q. Zhang et al., 2003). HPS5, however, is uniquely reported to have elevated cholesterol levels (Dessinioti et al., 2009; Wei, 2006).

There is a single report of a patient with HPS7, with a mutation in the dysbindin gene, *DTNBP1* on chromosome

**Table 1 | Subtypes of oculocutaneous albinism and syndromic albinism with associated genes and symptoms.**

| Disease | Gene | Symptoms |
|---|---|---|
| OCA<br>OCA1<br>OCA2<br>OCA3<br>OCA4 | <br>*TYR*<br>*P gene/OCA2*<br>*TYRP1*<br>*MATP* | OCA |
| HPS<br>HPS1-6<br>HPS7<br>HPS8<br>HPS9 | <br>*HPS1-6*<br>*DTNBP1*<br>*BLOC1S3*<br>*PLDN* | OCA, bleeding abnormalities, and lysosomal ceroid storage defects such as granulomatous colitis, pulmonary fibrosis<br><br>Immunodeficiency in HPS2 |
| CHS | LYST | OCA with silvery hair, bleeding tendency, peripheral neuropathy, immune deficiency |
| GS<br>GS1<br>GS2<br>GS3 | <br>*MYO5A1*<br>*RAB27A*<br>*MLPH* | OCA with silvery hair<br>Neurologic impairment in GS1<br>Hemophagocytic syndrome in GS2 |

**Abbreviations:** BLOC1S3, biogenesis of lysosomal organelles complex-1, subunit 3; CHS, Chediak-Higashi syndrome; DTNBP1, dystobrevin-binding protein 1; GS, Griscelli syndrome; HPS, Hermansky-Pudlak syndrome; LYST, lysosomal trafficking regulator; MATP, membrane-associated transport protein; MLPH, melanophilin; MY05A, myosin VA; PLDN, pallidin; OCA, oculocutaneous albinism; RAB27A, Ras-related protein 27A; TYR, tyrosinase; TYRP1 tyrosinase-related protein 1.

6p22.3, which encodes a component of BLOC-1; the patient presented with OCA, bleeding tendency, and decreased lung compliance (Li et al., 2003). HPS8 and HPS9 are also caused by mutations in BLOC-1. HPS8 is attributed to a mutated BLOC-3 gene (*BLOC1S3*) and is detected in a large consanguineous Pakistani family with incomplete OCA and platelet dysfunction. The proband was born with silvery hair that later darkened, hazel eyes, and pale skin that reddened in the sun (Morgan et al., 2006). HPS9 is associated with a mutation in the pallidin gene (*PLDN*), and clinically manifested with albinism and immunodeficiency in one patient (Cullinane et al., 2011).

A delay in diagnosis of HPS can be attributed to clinical variability (Torres-Serrant et al., 2010). Although hypopigmentation can be subtle at birth, nearly all patients with HPS have nystagmus (Gradstein et al., 2005). Early on, nystagmus is very fast and later slows as additional ocular abnormalities, such as wandering eye movements, become prominent. Typically, bleeding abnormalities initially present with bruising upon ambulation, but they may occur earlier with circumcision or trauma. One report detailed an infant who had a complicated delivery necessitating forceps and presented at 7 weeks old with seizures and associated subdural hematomas and retinal hemorrhages. The infant was found to have abnormal platelet function and was later diagnosed with HPS (Russell-Eggitt, Thompson, Khair, Liesner, & Hann, 2000). Epistaxis usually occurs in childhood, and prolonged bleeding with menses or after tooth extraction or any surgical procedure is typical. As ceroid accumulation increases with age, granulomatous colitis resembling Crohn's disease presents on average at 15 years old and occurs in 15 percent of cases, while pulmonary fibrosis typically does not become symptomatic until the patient's thirties and is usually fatal (Avila et al., 2002).

The diagnosis of HPS is established both clinically and via demonstration of absent dense bodies on whole-mount electron microscopy of platelets. Bleeding-time or platelet-aggregation abnormalities and tissue biopsy showing ceroid deposition may assist in diagnosis (Levin & Stroh, 2011). Sequence analyses for HPS1-8 mutations are available on a clinical basis and for HPS9 on a research basis only.

Given the bleeding risks in HPS, the platelet function of individuals with suspected albinism should be evaluated prior to surgical procedures. Although the bleeding diathesis is usually mild, death from hemorrhage has been reported (Theuring & Fiedler, 1973). In addition, bleeding in HPS has been controlled by administering desmopressin prior to surgery (Zatik, Poka, Borsos, & Pfliegler, 2002) and by making platelet concentrates available during surgery. It is important to be aware that aspirin and indomethacin are contraindicated in patients with HPS, as they exacerbate the platelet abnormality (Witkop, White, Gerritsen, Townsend, & King, 1973).

**Chediak-Higashi Syndrome**

CHS is a rare AR disease that is characterized by partial OCA with characteristic silvery hair and bleeding tendency, peripheral neuropathy, and immune deficiency (Dessinioti et al., 2009). This syndrome arises due to mutations in the CHS1/lysosomal trafficking regulator (*LYST*) gene, located on chromosome 1q42–43, which has roles in membrane identification and intravesicular sorting. Various vesicles are affected, and diagnosis is via visualization of pathognomonic giant peroxidase-positive cytoplasmic granules in neutrophils on a peripheral blood smear (Tomita & Suzuki, 2004). Abnormal granules can also be found in melanocytes, fibroblasts, endothelial cells, neurons, and Schwann cells, and

are formed through fusion, cytoplasmic injury, and phagocytosis (Nargund et al., 2010). CHS is distinguished by neutrophils defective in chemotaxis, mobilization, and bactericidal activity, and functionally defective cytotoxic T and natural killer cells. This results in recurrent pyogenic infections and uncontrolled T-cell and macrophage activation associated with a typically fatal hemophagocytic lymphoproliferative syndrome, considered the accelerated phase of CHS.

Most patients with CHS have a functionally null mutant CHS1 allele and manifest severe disease in childhood. At birth, patients may manifest OCA, exhibiting silvery hair and skin hypopigmentation, with cutaneous slate-gray patches and tanning capacity after sun exposure. Affected children may then develop recurrent infections of the skin, lung, and respiratory tract. The accelerated phase may occur soon after birth and is characterized by generalized lymphohistiocytic infiltrates, fever, jaundice, hepatosplenomegaly, lymphadenopathy, pancytopenia, and bleeding (Nargund et al., 2010). Ten to 15 percent of patients manifest adolescent and adult forms associated with missense-mutant alleles that encode proteins with partial function (Karim et al., 2002). These patients may survive to adulthood but develop progressive, often fatal neurologic dysfunction with intellectual decline, tremor, ataxia, peripheral neuropathy, and white-matter deterioration (Scheinfeld, 2003).

Although treatment of CHS is controversial, further investigation is critical in an individual with OCA and recurrent infections. Blood-smear examination leads to diagnosis and implementation of the only curative treatment, bone-marrow transplant, as fatality is within 30 months of the accelerated phase without treatment (Nargund et al., 2010). Other modes of therapy are controversial and include parenteral vitamin C administration during the stable phase in order to normalize neutrophils' bactericidal activity and high-dose methylprednisolone with or without splenectomy (Kanjanapongkul, 2006; Nargund et al., 2010).

### Griscelli Syndrome

GS is another rare AR disorder that manifests as partial OCA with characteristically silver hair, large pigment conglomerates in hair shafts, and accumulation of mature melanosomes within melanocytes (Mancini, Chan, & Paller, 1998). Defects in *MYO5A1* and *RAB27A* cause GS type 1 (GS1) and GS type 2 (GS2), respectively, and both map to 15q21.1. GS type 3 (GS3) is attributed to mutations in melanophilin (*MLPH*). *RAB27A* encodes a small GTPase protein, Rab27a, which targets the melanosome membrane and binds to melanophilin in melanocytes. Molecular motor myosin-Va, which is encoded by *MYO5A1*, is then recruited and permits movement of melanosomes along the actin cytoskeleton.

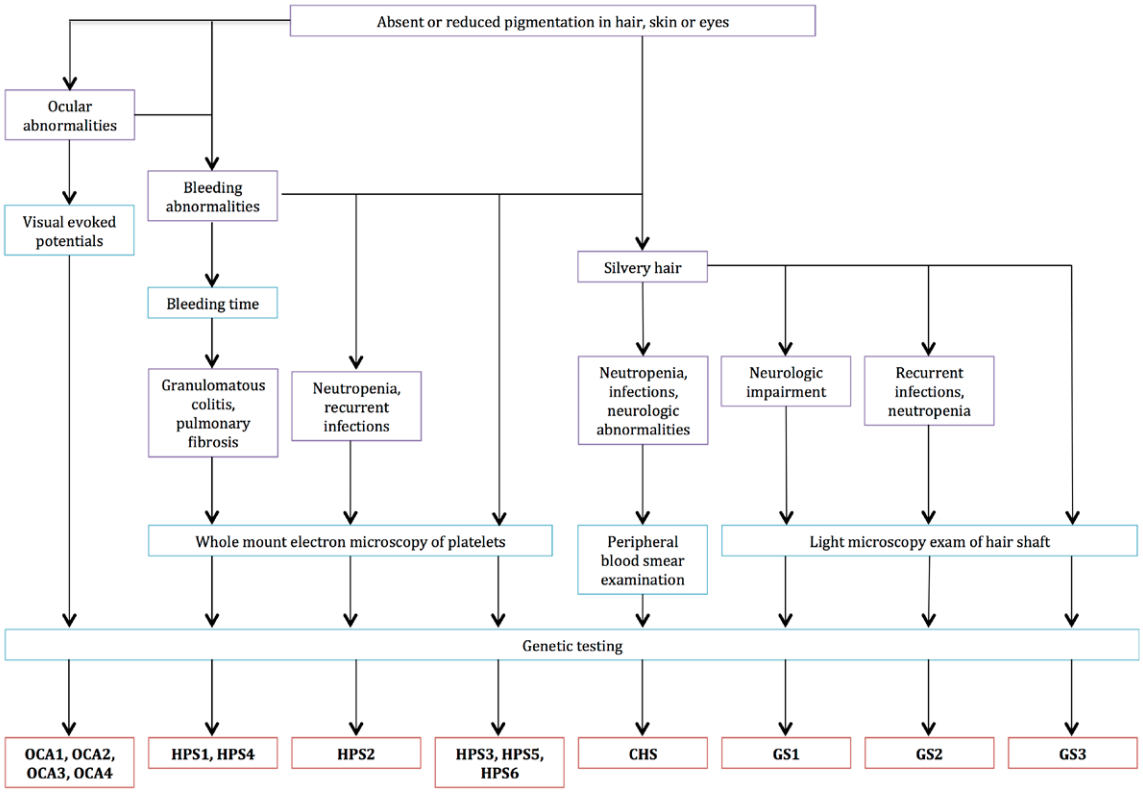


**Figure 2 | Diagnostic algorithm for albinism.** Based on clinical signs and symptoms and subsequent clinical and histologic studies and genetic testing, OCA, HPS, CHS, and GS can be diagnosed. Abbreviations: CHS, Chediak-Higashi syndrome; GS, Griscelli syndrome; HPS, Hermansky-Pudlak syndrome; OCA, oculocutaneous albinism.

The tripartite myosin-Va-melanophilin-Rab27a complex enables mature melanosomes to migrate to the dendritic tips of melanocytes, permitting delivery of melanin to adjacent keratinocytes (Al-Idrissi et al., 2010).

Patients with GS1 develop primary neurologic impairment that manifests as muscle hypotonia and intellectual disability, as myosin-Va has a critical role in neuron function (Sanal et al., 2002). In GS2, however, Rab27a is necessary in lymphocyte lytic granule release and lymphocyte homeostasis. Correspondingly, there is an uncontrolled T-lymphocyte and macrophage activation syndrome known as hemophagocytic syndrome (HS), which is associated with lymphocytic infiltration of organs and high mortality unless treated with hematopoietic stem cell transplantation (Al-Idrissi et al., 2010; Scheinfeld, 2003). HS may present in the neonatal period and is associated with preterm delivery (Lipton, Westra, Haverty, Roberts, & Harris, 2004). In contrast, GS3 is phenotypically restricted to characteristic hypopigmentation of the skin and hair.

Rapid diagnosis of GS can occur via light microscopy examination of a hair shaft demonstrating abnormal aggregates of pigment, permitting implementation of appropriate counseling and interventions according to the subtype. GS2 requires early diagnosis and preemptive treatment in order to prevent its severe complications (Wong & Yano, 2012).

## CONCLUSION

There is a limited differential of albinism, including few genetic syndromes with life-threatening consequences (Table 1). Diagnosis can be determined based on pedigree, review of systems, physical exam of skin, hair, and eyes, visual evoked potentials, and if indicated, skin biopsy, whole-mount platelet electron microscopy studies, blood smear, or hair shaft microscopy (Figure 2). Further, genetic testing via methods such as RT-PCR and genomic sequencing can confirm a diagnosis, as well as allow for prenatal testing and carrier detection (Falik-Borenstein et al., 1995; Santiago Borrero et al., 2006). With diagnosis, appropriate recommendations regarding ophthalmologic screening frequency, necessity for ocular muscle surgery, degree of sun exposure, and expectations related to systemic complications can be delineated. Delayed genetic counseling has been associated with poor academic performance in OCA, hemorrhage in HPS, and mortality in both CHS and GS (Torres-Serrant et al., 2010). With knowledge of the differential in conjunction with the execution of simple diagnostic tests, many of these complications can be predicted and consequently ameliorated or prevented.

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# Yellow Fever and the Emotional Consequences of Untreatable Epidemic Disease

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Yellow fever terrorized communities in tropical and urban settings during its height in the nineteenth-century American south. Carried by Aedes aegypti mosquitoes, which breed in stagnant water, the virus infects humans fervently and is most known for its symptoms of jaundice and vomito negro, a dark vomit of coagulated blood. During the near-annual outbreaks of yellow fever, caregivers struggled to cope with the emotional consequences of failing medicine, sometimes leaving behind clues to their confusion in treating the disease and offering salient reflections on their inadequacies. The disease ravaged the Gulf region for decades. Records of the health workers' feelings of futility reflect their questions of what to do for others and what to do for themselves, offering a new perspective on yellow-fever scholarship and insight into contemporary clinical practice and research.

## INTRODUCTION

Epidemic diseases often arise quickly, infect indiscriminately, and persist frustratingly. Once present, they can exist for years as untreatable medical and scientific quandaries. These threats to health may eventually be overcome, but only after years of scientific research, evolutionary advances in disease theory, successful experimental therapeutics, and effective distribution of curatives. The process is long and formidable.

As people progress toward the scientific understanding of diseases, particularly epidemic diseases such as yellow fever, which strike quickly and seasonally, they endure a period of confusion and trepidation before a resolution is found. Self-doubt, fear, and anxiety surface as mortality mounts. Evidence of these emotional reactions may be hidden under the guise of the emotional detachment demanded by the medical profession. Acknowledgments of medical, and sometimes personal, inadequacy remain concepts inferred from the words of social scientists and medical historians; scholars seem aware of these ideas, but they are seldom expanded upon or categorically defined.

Uncovering the hidden voices of workers in distress is a difficult task and requires significant good fortune on the part of the researcher. Stumbling across emotionally expansive letters or articles is not common when a researcher is scouring the early scientific literature and medical reports. But when such sources are discovered, salient remarks and pensive anecdotes can offer us a more complete understanding of an epidemic. Through close analysis, previously superficial knowledge about the emotional consequences of a disease takes on a new, more personal dimension, allowing a stronger connection between subject and observer. For the clinician or scientist today, such historical contemplation may help moderate the disappointment that can accompany attempts to combat disease. And such analyses of the past may help remove anxieties about failure; many people before us are shown to have failed on the way to success, thereby helping motivate innovative research unencumbered by apprehension.

Yellow fever has captivated social scientists for years, but the existing literature has not yet captured the sense of the disease's emotional consequences for workers who were on the front lines of disease control and treatment. The malady has inspired extensive scholarship by historians interested in the early public-health movements that arose because of the epidemic, the economic consequences of seasonal quarantines and the shutdown of city centers to limit the spread of the disease, and how it helped shape regional identities in warm-weather locations across the world (Humphreys, 1992; Bloom, 1993; Carrigan, 1994; Nuwer, 2009). I offer here a story with a different emphasis: the emotional consequences of an untreatable epidemic disease.

Sometimes known as "yellow Jack" or "bronze John," yellow fever terrorized communities in tropical and urban settings during its height. *Aedes aegypti* mosquitoes carry a virus that causes the disease; the mosquitoes breed in stagnant water, which was abundant in industrializing areas. A single bite transmits the virus to humans, initiating a gruesome infection. Hallmark symptoms include yellowing of the skin and eyes, known as jaundice, and expulsions of coagulated blood, or vomito negro ("black vomit" in Spanish). The details of transmission were unknown by observers of the disease in the 1800s; germ theory was still a novel idea, poorly received by the scientific community until the early nineteenth century. But the physical costs of the disease made it famous, as did its near-annual arrival in the summer months in cities such as Rio de Janeiro, Havana, New Orleans, and Memphis.

Throughout the American south, caregivers struggled to cope with their inability to treat yellow-fever patients. Unsuccessful treatments led to death, and successful ones were uncommon and inconsistent. One physician who experienced emotional turmoil in the face of widespread medical failure was Dr. William Armstrong, who worked for the Howard Association. His letters to his wife, whom he had urged to flee to Columbia, TN, during the epidemic, reveal

his frustration over the disappointing efforts he and his colleagues directed. His words, simultaneously depressed and determined, reflect his clear commitment to fight yellow Jack: "I feel sometimes as if my hands were crossed and tied and that I am good for nothing, death coming in upon the sick in spite of all that I can do" (Crosby, 2006, p. 74). Armstrong exemplified the thoughtfulness of those rare caregivers who have left behind a trail of personal letters and professional documents that describe their resolute but ineffective medical efforts.

Armstrong's feeling that his efforts were futile was characteristic of those felt by some caregivers in yellow-fever epidemics throughout the second half of the nineteenth century. Their concern was manifested on two levels: what to do for others, and what to do for themselves. The first level was characterized by the trial of different treatments, each with uncertain therapeutic value. The second reflects the sense of helplessness made up of fear, isolation, and loss of faith in cures. Together, these responses complicated the efforts of healers to treat yellow fever and further weakened an already fragile medical and regional community.

For today's physician, nurse, health worker, or scientist, the story of these century-old epidemics should offer solace to the overworked and inspiration to the distressed. Tales of pain, failure, and inadequacy are not new developments confined to the modern healthcare system; they are recurring themes for those faced with, and called on to prevent, disease and death.

## THE QUESTION OF TREATMENT: WHAT TO DO FOR OTHERS

In 1879, a Kentucky physician by the name of J. P. Dromgoole published a long book cataloging the many opinions of physicians in response to the yellow-fever epidemic of the previous year. In 1878, according to one tally, twenty thousand lives were taken by the disease (Cirillo, 2010). Dromgoole's work, *Heroes, Honors, and Horrors,* is a collection of caregiver practices and contemplations, a comprehensive compilation of medical workers' experiences during the outbreak. The purpose of the book, according to its author's dedication, was to honor the "clergymen, physicians, and nurses who, in the hour of need, rushed to the relief of suffering fellow-men." It highlights articles and letters by, and biographies of, those heroes who strove to rid the United States of yellow fever. The work, through its assembled documents and contextual analysis, effectively captures the sense of uncertainty about the yellow-fever epidemic, and it reveals how healers focused on therapeutics rather than disease etiology during the yellow-fever outbreaks.

Southern scientists and physicians felt that the prevalence of disease was a consequence of the region's climate, germs, and Caribbean trade. The south seemed a particularly unlucky place in the nineteenth century. During the years from 1863 to 1883, roughly 6,500 New Orleans residents died of smallpox. In 1850, 47.5 out of 1,000 deaths in the United States resulted from malarial fevers, many of which occurred in the south; there, warm, wet summers helped fuel mosquito reproduction (Hong, 2007). Yellow fever made the most impressive mark throughout the century with frequent but inconsistent large-scale epidemics resulting in 41,000 deaths in New Orleans alone from 1817 to 1900 (New Orleans Public Library, 2003). The prevalence of the disease and its death tolls prompted southern scientists to develop a regionally exclusive perspective on disease and treatment.

Constantly plagued by warm-temperature maladies such as yellow fever, physicians and scientists in the south had historically designated their region medically distinctive; they felt that regionally specific diseases required unique treatments. Medical distinctiveness, a concept created by southern physicians, claimed that regional factors such as climate, economics, and even racial demographics made the south a breeding ground for anomalous maladies (Leavitt & Numbers, 1978; Savitt & Young, 1988; Stowe, 2004). Dromgoole's *Heroes, Honors, and Horrors* addresses the "Tidal Wave of Death and Destruction," with "Historical Sketches of Each Afflicted Locality"; the first chapter discusses yellow-fever symptoms, treatments, and explanations.

Southern medical specialization started with southern medical education. Disease in the south demanded regional medicine, according to experts at the time, and that way of thinking shaped the minds of local physicians. No matter what opportunities existed elsewhere, students tended to seek education from local institutions. One student chose to study in Charleston because "we know better, here, how to manage Carolina constitutions than the Physicians of Philadelphia" (Warner, 1989, p. 193). Philadelphia was renowned for its medical centers; the city hosted the nation's first public hospital and medical school, making the College of Physicians in Philadelphia one of the most respected medical centers at the time. The outspoken student's father, also a physician, echoed his son's themes in a subsequent letter, claiming that climate, miasmatic exhalations, diet, dress, work habits, and social structure altered the symptoms of diseases and appropriate therapeutics in ways not understood by non-natives. Region-focused medical dogma drove practitioners to train in the south.

The expression of medical distinctiveness took several forms, one being an ongoing discourse between the south and the north about the validity of the concept itself. As southern scientists proclaimed themselves especially sensitive to the south's exceptional scientific needs, northerners argued to the contrary. Northern scientists and physicians used the recurrence of disease and high mortality rates from diseases such as the incessant and deadly yellow-fever outbreaks to bolster their claim that the south's undeveloped backwoods and dirty cities predisposed southerners to disease, making southern "experts" merely unwitting promoters of their own region's ill health. Those in the south responded passionately, claiming that the critics were unfamiliar with the dangers of southern maladies and therefore unfit to judge the southern plight.

Sure of his regional expertise and the inability of northern-

ers to survive the yellow-fever season in Tennessee, the president of the Memphis Board of Health turned away volunteers from the north in 1878, the deadliest epidemic year in the Mississippi Valley (Crosby, 2006). His primary motive, according to one commentator, was to limit the strain on the Memphis caregivers during an epidemic in which 17,000 of the city's citizens became infected; Memphis needed better help and fewer casualties, not an influx of unprepared and unspecialized physicians and nurses (Crosby, 2006). This example shows how those in the south existed in an environment of entrenched exceptionalist medicine and science, due in part to a south-north debate, and acted accordingly.

Others supported the notion of medical distinctiveness by actively recruiting local health workers during the epidemics. The Howard Association, a charitable organization founded by British philanthropist John Howard, implanted itself in the Gulf Coast region during its nineteenth-century battles with yellow Jack (Newsom, 1992). Besides sprouting infirmaries, hospitals, orphan asylums, and fund-raising efforts across the afflicted states, the Howard Association often helped promote regional health cooperation. In 1878, a year when Houston was not affected by yellow fever, a Howard nurse by the name of Kezia Payne DePelchin answered a call from Memphis for nurses. She proceeded to Tennessee to aid her fellow southerners and offer her medical expertise. Trained in the south and familiar with yellow fever through Houston's frequent bouts of the disease, nurse DePelchin embodied the kind of local proficiency preferred during yellow-fever epidemics.

Though they proclaimed themselves medically distinct, southern health workers lacked uniformity in their practice, often prescribing conflicting treatments in line with their personal experiences. In general, treatments fell into four categories: hydropathic, homeopathic, botanic, and orthodox. Hydropathy used water as an internal and external healing factor, applying large or small amounts as the situation suggested. Homeopathy focused on the natural ability of the human body to fight disease and employed diluted medicines to aid the process. Botany relied on herbs and plant-based concoctions for patient recovery. Orthodox medicine used drugs and substances such as quinine, calomel, teas, alcohol, opium, and bloodletting to alleviate the suffering of the sick (Humphreys, 1992; Bloom, 1993; Carrigan, 1994). Often, a practitioner's methods did not exclude any of these treatments. The therapeutics offered by medical workers ranged widely, as no treatment proved predictably superior to another. The blending of treatment techniques allowed for much experimentation, though variance in treatment failed to improve patient prognosis significantly.

A snapshot of the treatments used by caregivers in Dr. Dromgoole's *Heroes, Honors, and Horrors* reveals the diversity of the treatments given to patients. One physician described a "Creole treatment" he administered; the name saluted the French Louisiana region, and the treatment called for an eleven-step plan that included doses of castor oil, hot footbaths, sponge baths, injections of laudanum, watermelon-seed teas, cool cloths on the head of the patient, chicken broth, and the directive that the patient not be allowed to sit up for a week (Dromgoole, 1879). Such treatments as this were common but, alarmingly, unique to each physician's clinical experience. Another doctor recommended a "calomel remedy," which combined footbaths and chicken or beef broth. One doctor recalled how he made a complete recovery from a bout of yellow fever by drinking ice water, bathing in ice, and resting (Dromgoole, 1879). Footbaths and broths were recurrent themes in treatment, despite their varied interpretation and application by physicians; no distinct and unanimously accepted treatment arose.

The Creole treatment, calomel remedy, and ice treatments were consistent in treating fever by using broths and baths as hydropathic remedies. However, other suggested solutions took entirely opposite stances. Mrs. Jane Swisshelm, a nurse, claimed that ice was detrimental to some patients and likely even accelerated death by reducing the patients' body temperatures too severely (Dromgoole, 1879). She argued that warm water opened the pores of the patients and drew out the poison of the fever contained inside the patients' bodies, allowing for timely and safe recovery. To support her claim, she referenced conversations she had with "prominent doctors in this country" and the case of a military officer who self-administered the warm-water treatment and overcame the malady (Dromgoole, 1879). Mrs. Swisshelm exemplifies a common trend among healers: their unshakable confidence in their own techniques. Her self-confidence, as well as the criticism she offered of different techniques, reflects the inconsistency in fever treatment and, by extension, the breadth of the yellow-fever problem. As confusion reigned, clashes within the medical community surfaced.

Professional healers were not the only group promising therapy. Lay healers commonly applied home remedies to loved ones, further complicating treatment. Like the professionals, these caregivers used a variety of techniques to treat yellow-fever patients, with enough success to give them a superficial confidence in their approaches. But these home remedies, too, were generally ineffective. Imagine, then, the frustration of locally trained caregivers using nearly every conceivable treatment to resolve the relentless outbreaks, but continuing to disappoint themselves and, more importantly, their patients. This frustration immersed the entire Gulf Coast region, linking distinct locales together in their struggle for reprieve.

Nurse DePelchin described Dr. Dromgoole's work as a nearly encyclopedic source for fever-treatment options. During her stay in the Mississippi Valley region, she wrote extensive letters to her sister. The letters continued after the end of the epidemic, and one dated March 1, 1879, directly validated *Heroes, Honors, and Horrors* as a compilation of approaches to fever treatment and its related disappointments. In her words, the book served as a "very good illustration of the various ideas that prevailed and which nearly all failed" (DePelchin, 1879). Seemingly prompted by the book, she offered a lengthy description of the varied treatments she had witnessed in her time as a Howard nurse for fever

patients at different points during the illness. DePelchin's invaluable letters give credence to Dr. Dromgoole's work as a respected summary of yellow-fever treatments and a catalogue of their ineffectiveness.

In sum, the wide variety and promised quality of individual fever remedies intensified the treatment question. As Dr. Dromgoole's book showed, little was agreed upon by scientists, and when agreement was reached, as on the use of water as a curative, the details remained highly disputed (e.g., the temperature of the water). So yellow fever thrived during this era of confusion for southern caregivers. Disappointment was the result, and it affected the caregivers in distinct ways.

## FEAR, LOSS OF FAITH IN CURES, AND ISOLATION: WHAT TO DO FOR ONESELF

From the wreckage of the yellow-fever epidemics of the nineteenth century emerges a previously understudied notion of professional futility in yellow-fever medicine. Personal reflections and articles written by medical workers in response to their failures to remedy yellow fever suggest that a group of aware but helpless medical workers existed. Their reflections fall into three categories: fear, isolation, and loss of faith in prescribed treatments. The caregivers' contemplations show how the shared dilemma of yellow fever in the American south affected the entire medical community, despite notions of regional exceptionalism. And as some medical workers turned to religion for support, yellow fever appeared to be a malady uncontrollable by humans.

One of the most deadly yellow-fever epidemics to hit Galveston, TX, left behind a fearful story of physicians realizing and understanding their mortality. The year was 1867, and amid the climbing death tolls that eventually took nearly one of every four citizens of the port city, a doctor named George Taylor became one of the many who sacrificed his life for the benefit of others (Ratchford, 1945). In letters to his wife, whom he had left behind when he went to work in Galveston, fear pervaded his thoughts. The mundane nuances of his daily routine and sad longing for his wife were interspersed with recounted conversations with his peers that centered on trepidation about the onslaught of another fever season. Taylor notes how once-confident caregivers shrank under the realities of an underestimated epidemic: "Men who talked very loudly and fearlessly when they did not believe there was any [fever] here, are now frightened out of their wits" (Ratchford, 1945, p. 37). In Galveston that year, Dr. Taylor died alongside several companions in the fight against yellow fever. Mortality, described by a martyred doctor in 1867, raised the stakes of fever treatment and frightened otherwise confident medical workers.

The death of medical workers from bronze John was widely noted by historians and contemporary health workers. Of the three thousand Howard Association nurses in the 1878 fever epidemic, one third died. Of 111 Howard doctors, 54 contracted the fever and 33 died (Crosby, 2006). Dr. Dromgoole offers a three-page, four-column list of all the physicians, military personnel, and ministers who died serving fever patients in 1878 across the nation, a list to which DePelchin added another five with whom she had direct contact (DePelchin, 1879). The sheer magnitude of the caregiver mortality described by these sources, totaling approximately 350 in 1878, illuminates the cost of failed treatment paid by all people in the region, regardless of medical training.

As caregivers faced death in their work environment, the recognition of their inadequacies as healers of both patient and peer became more pronounced. Nurse DePelchin experienced persistent feelings of inadequacy as she aided physicians in the fight against yellow fever. In letters written to her sister, references to these sentiments abound. In one letter, she described the difficulty of her work and the emptiness she felt when failing to save a dying patient. Addressing her attending physician, she asked, "What makes me so unlucky?" He replied appropriately, considering the glum realities of caregiver success rates for ill patients, saying, "This fever baffles and staggers the wisest" (DePelchin, 1878). The daily mortality faced by caregivers pushed them beyond the science they understood and the treatments they administered. They exhibited a loss of faith in the existing, and often conflicting, treatments.

Some caregivers addressed their inadequacy directly. Prominent New Orleans physician Joseph Jones criticized reliance on the unconfirmed techniques of yellow-fever prevention by arguing that others had simply not admitted the truth of the limitations on medical knowledge about the fever. Reaching his breaking point, Jones declared, "I am thoroughly convinced that we have discovered no antidote or abortive treatment for the disease, and since, I have abandoned the use of powerful remedies" (Jones, 1879, 651). By abandoning the standard remedies and acknowledging the lack of antidote for yellow fever, Jones boldly suggested his distrust of his own medical efforts to eliminate the disease. He was not the only one to do so. A Little Rock physician similarly proclaimed his distaste for existing remedies and professed, "I have learned a great deal about the fever since it broke out here, and have found that in every case patients do better without medicine" (Dromgoole, 1879, p. 51). Physicians who publicly disowned available fever therapies represent an important faction of caregivers who refused available methods, finding them unreliable. Their lack of faith in existing remedies went hand in hand with the fear caused by unyielding seasonal bouts of the malady and the realities of patient and caregiver mortality.

While some lamented their failures in personal reflections, others instead opted to risk their lives to find a cure by self-medication and infection. These individuals performed experiments they believed to be beneficial to the medical community and sought to uncover the causative factors of the disease and better understand its operation. Their audacity reflects their loss of faith in existing remedies. Two instances of self-experimentation come from the notes of New Orleans physicians James Carroll and Alcée Chastant. According to Carroll, one medical student in Pennsylvania, perhaps eager to resolve a disease southerners could not,

experimented on himself by placing fresh black vomit and blood serum obtained from yellow-fever patients into wounds made in his arms and legs. The student also inhaled the fumes from black vomit and made black vomit into pills and swallowed them (Carroll, 1905). In Chastant's case, a fellow physician also applied black vomit to the surface of a cut made on his arm, swallowed a quantity of the substance, inhaled fumes obtained by evaporation of the matter, and inserted some into his eyes. Such self-experimentation, however laudable, further identifies yellow-fever caregivers as a group desperate for a cure. Though the experimenters' precise motivations are not clear, the grim realities of mortality and unsuccessful treatments likely played a role.

Faithlessness in existing caregiver remedies opened discussion of yellow fever as self-limiting, a concept that signaled personal defeat for scientists and healers amid continuing patient deaths. Dr. Samuel Choppin of New Orleans once admitted that no limits placed on the disease by humans could prevent the disease's transmission or course. Arguing that the medical community could do nothing to reduce the impact of the disease, Choppin said, "We are at a loss to know how to check the ravages of the fever when it attacks the human body" (Dromgoole, 1879, p. 71). Pessimism from lost faith pervaded the minds of prominent physicians such as Choppin in their efforts to check the onslaught of the disease. Remarking how little done by caregivers improved the likelihood of survival, DePelchin once compared the unchecked rampage of yellow fever to that of a tornado sweeping through a beautiful town (DePelchin, 1878). A fine comparison, the image of a tornado ravaging the town aptly evokes the unbridled and uncontainable havoc caused by yellow Jack. For medical workers during the summer months, resolving the yellow-fever dilemma in the south may have appeared as fruitless an endeavor as attempting to stop a tornado.

In the late nineteenth century, caregiver isolation was not fueled solely by failed medical experiments and remedies. The realities of patient care and the likelihood of death for these caregivers increased their loneliness. Although a plethora of forums existed in which they could discuss general understandings, treatments, and yellow-fever policies, medical workers suffered from solitude as their work created—and demanded—emotional detachment. Few answered the call to tackle the dilemma on the front lines. Those who did witnessed unchecked disease fatality. For the caregivers in this setting, failure left them psychologically vulnerable to solitude from detachment and physically vulnerable as their peers perished. This isolation fueled, in some caregivers, a reliance on religion, with God being the only reliable source of comfort.

Understanding the caregivers' isolation starts with understanding the level of exertion their work demanded. Forced in some cases to see more than one hundred patients a day, doctors in the plagued city centers frequently surpassed their requisite duties to ease the suffering of the populace. Others simply heard begging and pleading from the ill as the doctors passed from house to house but were forced to continue onward, answering awaiting appointments for house calls. Spending several nights in a row without sleeping or eating affected the minds of the patients as well as of the bedside caregivers; as the illness set in, it caused irritability and restlessness, a combination that could make patients turn maniacal and demand much attention, refusing caregivers any respite (Crosby, 2006).

Working in understaffed conditions and personally overextended, yellow-fever caregivers suffered from widespread physical and mental dilapidation, which enhanced their emotional fragility. Forced sometimes to bury their own patients due to poor funding and high mortality, particularly in smaller towns, some caregivers developed a sense of callousness. The nurse Kezia DePelchin described the experience of having to bury several children in Senatobia, MS, as one from which she initially demurred, but to which she eventually became desensitized (DePelchin, 1878). In this case, detachment from compassion in the face of death, particularly for a very emotionally aware woman such as DePelchin (as evidenced in her insightful letters to her sister), proves the detrimental effect of failed efforts to save patients. Futility caused her continuous emotional strain and altered her perspective on the dying. The work, damaging and unrelenting, siloed DePelchin into a world of complex emotions where endless strain fueled an opposite, but requisite, detachment.

On a cool winter night in Memphis, Dr. William Armstrong foresaw the end of the 1878 fever season and reflected on the loss of colleagues by commenting on his solitude. "My heart abounds with joy," he wrote, "at the mere hope that this cool night will possibly end our labors. . . . I alone am standing" (Crosby, 2006, p. 82). The words of Dr. Armstrong speak to the impact of the work demands and the emotional drain on healers in the American south. What remained for a physician or nurse or minister who sacrificed so much over several months, only to see patients, friends, and coworkers perish? The respite of the fever's end calmed Dr. Armstrong and others, but at what personal cost? He had survived the fever (he was infected, but overcame the malady), served others (many of whom did not survive), and abandoned his family (left in the countryside of Tennessee) to treat a disease that, in the end, he was no better off at managing than at the onset. Despondent and broken, faced with personal and professional futility, and surrounded by beneficent societies, some caregivers turned to religion for emotional security and reassurance.

In the nineteenth-century American south, Christianity was dominant. When faced with professional and personal strain as a result of epidemic yellow-fever outbreaks, some caregivers looked to religion for emotional support. In many cases, Christian fellowships and covenants led the push for patient care. In New Orleans, the Sisters of Charity, the Sisters of the Holy Family, and later, the Italian Sisters of the Sacred Heart worked to secure funding and care for the suffering (Carrigan, 1994). In Memphis, St. Mary's Cathedral functioned as an orphanage for children with sick or deceased parents (Crosby, 2006).

DePelchin left behind a clear trail connecting medical futility to religion in the yellow-fever epidemics of the nineteenth century. One for artful descriptions of her thoughts, DePelchin relayed important trends for Christian caregivers at the time. In October 1878, for instance, she wrote to her sister wondering if God heard her when she prayed. Saying "I have prayed more than in all my life put together," DePelchin exhibited a reliance on religion during her stay as a Howard nurse (DePelchin, 1878). Many embraced connections between science and religion, as ministers believed scientific discoveries would confirm the dogmas of Christianity. As one historian put it, "Few people in the South outside the ranks of physicians and scientists could have exhibited greater enthusiasm for natural science than did the southern clergy" (Holifield, 1989, 127). As science failed her and her patience disappeared, DePelchin turned wholeheartedly to Christianity. Religious faith, for DePelchin and others, provided a break from the inadequacies of medical practice during epidemics.

The inclusion of several sermons delivered in fever locales during the 1878 epidemic in Dromgoole's *Heroes, Honors, and Horrors* affirms the role played by religion for fever healers and patients alike. One such sermon, given in Louisville by the Reverend H. C. Morrison, begged the members of the congregation to consider the faith they put in science, stating that science had become a form of idolatry for those (both caregivers and the ill) awaiting the arrival of the season's first frost to free them from the epidemic. To show the faults of fever sufferers' idolatry, Morrison cited the prophet of God who prayed for water and received it, despite nearly four years of "brassy heavens" and ignoring the "natural indications" of continued drought. "And yet we pray," he argued, "and the elements are not changed, and why? He [the prophet] had faith, while we have not" (Dromgoole, 1879, p. 55). Using the metaphor to make his point, Morrison encouraged the listeners to put less faith in science and more in religion. This sentiment echoed the reflections of DePelchin and certain other caregivers suffering from emotional distress. Trust religion, not science, these Christians argued, when faced with an affronting and uninhibited disease.

## CONCLUSION

Religion may have offered caregivers a sense of reprieve from their scientific blunders, but in the end, the effect of yellow fever was more exact than could be determined by theories, experimentation, or religious faith. DePelchin made clear the lasting effect of the 1878 epidemic and the internal struggles that followed. After the outbreak had passed, she wrote, "still the remembrance of the awful scenes of the great epidemic have cast a shadow on my heart that will never pass away" (DePelchin, 1878). Faced with daily instances of failure and doubt, caregivers were unable to escape the reverberating emotional damage caused by the epidemic. Regardless of the methods undertaken for examining the disease's transmission, proper treatment, or eventual end, those who experienced its wrath suffered from a distinct sense of helplessness in dealing with the malady and its toll. Fear, loss of faith in remedies, isolation, and reliance on religion characterize the emotional consequences for caregivers unable to stop the disease's wrath. These themes may echo the experiences of clinicians, researchers, and caregivers in today's healthcare community, particularly in the context of unyielding, unexpected, and untreatable disease.

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