Published in final edited form as:

J Health Care Poor Underserved. 2015 August ; 26(3): 648–661. doi:10.1353/hpu.2015.0094.

The Effect of Structural Violence on Patients with Sickle Cell Disease

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Abstract

Sickle Cell Disease (SCD) is a burdensome and prevalent condition predominantly seen in populations of African heritage. Treatments for SCD, particularly those related to pain crisis, are largely insufficient. We argue that it is through structural violence—a systemic series of policies, institutions, and practices—that individuals who live with SCD suffer from health disparities. Similarly, we argue against other suggested mechanisms and causes, such as purely economic factors or low public interest and knowledge. We shall do this in part by comparing the systemic response to SCD to that of Cystic Fibrosis (CF), another genetic based illness with similar prevalence. Notably, CF that affects a very different target population, and has very different research, funding, and treatment trajectories. Underlying these arguments is the hypothesis that structural violence can harm a population in a developed nation just as it can in a developing one.

Keywords

Sickle cell disease; sickle cell anemia; structural violence; research support; health care disparities

The phrase *structural violence* describes how a society, its structures, and its practices systematically harm, even exploit, certain individuals or groups. Paul Farmer states that:

...I use this term as a broad rubric that includes a host of offensives against human dignity: extreme and relative poverty, social inequalities ranging from racism to gender inequality, and the more spectacular forms of violence that are uncontestedly human rights abuses, some of them punishment for efforts to escape structural violence...¹

The word, *violence*, is used to reflect the damaging consequences to individuals and groups when unjust structures, policies, and practices permeate a society. On a population level, people with Sickle Cell Disease (SCD) suffer from high rates of morbidity and mortality, low quality of life, and short life expectancies.² We shall argue that it is through structural

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violence—a systemic series of policies, institutions, and practices—that individuals who live with SCD suffer from health disparities and not from other suggested mechanisms and causes, such as pure economic factors or low public interest or knowledge.³ It is through this argument that we demonstrate that the concept of structural violence is operational not just in resource-poor nations, in terms of which the concept arose, but also in resource-rich settings.

Structural Violence

Structural violence is a phrase that reflects the ways in which society's structures, systems, and policies affect the well being of individuals and groups in a negative and unjust manner. For example, in a region of southern Thailand where the residents are primarily of low socioeconomic status, increased rates of lead exposure have been noted in children; these exposures were linked to the presence of nearby boat facilities.⁴ In this case, policies such as inadequate regulation of the lead waste from these facilities contributed to the lead poisoning among these children.

Analyzing inequities through the lens of structural violence puts our focus on systemic policies and practices, and the ways these affect individuals. Jeffrey Sachs, for example, relates the concept of structural violence to the ongoing malaria epidemic:

Household spraying, insecticide-treated bed nets, and antimalarial medicines all work in Africa just as they do in other parts of the world...No children need to die, and none will if they have access to all of the modern tools of disease prevention and treatment!⁵

Sachs' point is that high morbidity and mortality due to malaria in Africa is in large part due to the lack of access to existing prevention and treatment methods. As noted by Snow et al., funding in 2010 for worldwide malaria control was 60% below the estimated 4.9 billion U.S. dollars (USD) needed, or just under two billion USD.⁶ In this example, structural violence results from the financial priorities (forgoing malaria funding donations for other expenditures such as military spending, domestic infrastructure, or some other cause the potential donor's system of governance favors) or ability of donor countries to donate funds.

In this essay, we argue that the primary reason for inequalities suffered by SCD patients is structural violence, and demonstrate its operation even within resource-rich contexts.

Sickle Cell Disease

The primary reason for the absence of effective medicines in treating many neglected diseases is controversial and probably multi-factorial; however, there is a growing consensus that effective treatment options for these diseases are lacking because such endeavors are seen as unprofitable.^{7,8} It should be noted that when one speaks of neglected diseases, one often is referring to the list delineated by the WHO,⁹ which includes mainly infectious diseases.

We argue that SCD ought to be thought of in the same way. While SCD may not be as prevalent worldwide as some of the diseases on the aforementioned WHO list, it is relatively

and substantively neglected in terms of attention and research dollars worldwide when compared with other conditions having similar prevalence. We argue that SCD is a “neglected disease” not because there simply is insufficient money or profits available to research SCD or that it is a low prevalence condition, operating under the usual forces for an orphan disease¹⁰ but, rather, that SCD treatments have progressed little because of economic and racially motivated factors properly grouped together under the rubric of structural violence. While Smith et al. note the possibility that race may play a factor in the lack of funding for SCD research,¹¹ we advance an argument attributing the lack of funding for SCD research as well as other inadequacies in SCD treatment to structural violence.

Epidemiology and Clinical Features

Sickle cell disease is primarily a genetic disease of minority populations in the United States, while Cystic Fibrosis (CF) is a genetic condition that primarily affects Whites; here, CF will be used as a contrast to SCD. Given that the prevalence of each of these inherited diseases are similar, that both conditions have significant morbidities and mortalities associated with them, but that they affect very different populations in terms of race and socioeconomic status, we choose to compare the two conditions in terms of treatment and research devoted to each.

In the United States there are approximately 100,000 people affected with SCD.¹² This disease affects one in 400 African Americans and one in 19,000 Latinos.¹¹ In comparison, CF affects about 30,000 individuals in the United States,¹³ affecting one in 3000 caucasians, one in 4000-10000 Latinos and one in 15,000-20,000 African Americans.¹⁴

Sickle Cell Disease is a condition characterized by a mutated hemoglobin molecule that makes the red blood cell susceptible to transforming to the abnormal sickle shape under certain conditions. Its manifestations can include severe sickle cell pain crises, acute chest syndrome, retinopathy, renal failure, chronic lung disease, and early death along with many other presentations.¹⁵ In contrast, CF is characterized by a mutation in the CFTR gene causing a defective chloride channel, which results in thickened secretions. These secretions lead to a variety of ailments including respiratory disease characterized by recurrent infections and bronchiectasis, pancreatic exocrine insufficiency, and infertility to name a few of the more common manifestations.¹⁶

In the Cooperative Study of Sickle Cell Disease (CSSCD) 12,290 pain episodes were documented in 18,356 patient-years, or approximately 0.67 pain episodes per patient year. However, it has been established that pain crisis prevalence is often underestimated as patients often attempt to manage their symptoms at home.¹⁷ Balas et al. noted that an average pain crisis required 7.5 days of hospitalization and 50% of these episodes required readmission to the hospital within one month.¹⁸ Knowing that approximately 100,000 individuals in the United States are afflicted with SCD, we can then calculate that SCD pain crises result in 502,500 days of hospitalization nationwide. Furthermore, 11% of patients with SCD suffer a clinically significant stroke by 20 years of age, and 24% by the age of 45.¹⁹ In addition, one study of SCD patients showed median survival of 42 years of age for

males and 48 years of age for females, most persons during an acute pain crisis, acute chest syndrome, or stroke.²⁰

Turning to CF, most morbidity and 90-95% of mortality is due to chronic pulmonary infections and their associated pulmonary exacerbations.^{21,22} Pulmonary disease related to CF is generally characterized by progressive disease accelerated by exacerbations. These exacerbations may include increased cough, sputum production, dyspnea, chest pain, weight loss, anorexia, and lung function decline.²³ One study noted that pulmonary exacerbations were associated with decreased health-related quality of life scores (physical and psychosocial categories).²⁴ The average pulmonary exacerbation results in an average hospital stay of 8.7 days.²⁵ Additionally, in a study of 11,692 patients, 4,881 (42%) had at least one exacerbation in a period of six months. Further extrapolating this data to the 30,000 patients with CF, an average of 12,524 pulmonary exacerbations occur per six months. This translates into approximately 109,000 hospital days per six months in the United States,²⁶ or approximately five times less than is seen with SCD. Finally, it should be noted that medial survival for persons with CF is 37 years of age as of 2008, up from 32 in 1999 and that 76% of patients eventually die due to progressive respiratory failure²².

Treatment Options

Hydroxyurea is treatment that has been shown to decrease frequency of sickle cell pain crises.²⁷ Despite its efficacy, many concerns exist surrounding the use of hydroxyurea in SCD including ineffectiveness in some patients and the theoretical risks of mutagenesis and teratogenesis.¹⁵ Blood transfusion is another option designed to decrease cell sickling but is typically used only as a last resort.²⁸

Stem cell transplantation is designed to cure SCD. These treatments have reported excellent results in selected patients;²⁹ however, at this time the technique has primarily been used in children (approximately 200 in total) with HLA-matching siblings. More limited experience has been accrued with adults.³⁰ Although less intense myeloablative regimens have been used more recently,³⁰ overall, there is a 5-10% risk of death.³¹ Additionally, the cost of these procedures makes them prohibitive to many patients.

To date, most sickle cell crises are treated in the same manner that they have been treated for many years; with oxygen, IV fluids, pain management, and antibiotics (to treat associated infections) being the mainstays of treatment. In addition, patients with acute pain crises may experience significant delays in pain control both in terms of time to analgesic administration and in terms of wait times prior to being seen compared to other populations.^{32,33}

Treatments available for CF pulmonary exacerbations have evolved considerably in recent years. Antimicrobials are now used through both traditional IV and oral forms as well as through inhalation.³⁴ In addition a number of therapies have been designed to help the patient with mucus clearance such as Dornase alpha, chest physiotherapy, and nebulized saline.³⁵ Quality improvement benchmarks have also become an emphasis in caring for people with CF.³⁶ This combination has greatly improved quality of life and life expectancy.

Available Research

Thirty five NIH-sponsored studies are currently recruiting patients for clinical trials involving SCD compared with 29 NIH studies currently recruiting patients for CF.³⁷ This information is publically available at www.clinicaltrials.gov and can be obtained via the advanced search option and the terms “sickle cell disease” and “cystic fibrosis” while narrowing the search for those currently recruiting patients and those with NIH funding. If the search includes studies from all funder types (e.g. not limited to NIH funded), 135 studies are listed for sickle cell disease while 202 studies are listed for cystic fibrosis³⁷. While this does not reflect the quality of these studies, their potential significance, or the number of proposals overall; the total number of studies for each indication does give some indication about the active research in these areas. Interestingly, while there are more NIH funded studies examining SCD at this time, overall studies favor CF. Additionally; when an Ovid® search is conducted for the key word Sickle Cell Anemia, 17,339 results return whereas 27,547 results are obtained for the key word Cystic Fibrosis. When the search is narrowed to randomized controlled trials; 705 results are found for Cystic Fibrosis; Sickle Cell Anemia yields 240 studies.³⁸ The discrepancy is striking given the relative prevalence of these conditions; however, the exact reasons for this difference is not definitive as there are numerous other possible explanations for such a complex phenomenon as we are addressing. These can include, for example, differences in the biology and pharmacology of each condition, biologic and other differences in the constituencies, or even the system of development, barriers, and rewards that scientists experience. Again, it is not our assertion that structural violence is the only explanation for this discrepancy; only that is a significant contributor that has not been addressed in the past.

While it should be noted that there are dedicated investigators attempting to reduce mortality and morbidity for patients with SCD, the amount of research and drug development pales in comparison with CF, a disease with one third the prevalence of SCD. Moreover, this discrepancy is not due to a lack of patient interest in participating in research, as previous large studies such as the CSSCD demonstrate.

Financing Research and Improved Treatment

In 2012 the NIH reported spending \$65 million on SCD (which affects over 100,000 individuals in the U.S.) across all of its institutes, while spending \$86 million on Cystic Fibrosis (which affects 30,000 individuals in the United States) over the same time period.³⁹ In addition to government funding, many private organizations fund health-oriented research. For instance, in the last years that data are available for both organizations (2012), the Sickle Cell Disease Association of America (SCDAA) received \$905,835 in philanthropic support and grant income⁴⁰ while the Cystic Fibrosis Foundation (CFF) received \$134,090,038.⁴¹

The private foundation financial information may simply represent the relative wealth of those affected by these diseases or those who are most interested in seeing successful research about these diseases [author: or might it represent ongoing progress or some other reason orthogonal to the line of reasoning implied here?]. Admittedly, ~~this is another rough~~

measure as many other factors may be contributory; however, the disparity between the donations is striking and perpetuates the disparity of care for the two populations.

Characteristics of the SCD Constituency

It is not the wealthy, nor the majority racial/ethnic group that bears the brunt of SCD; rather, people of African descent are most commonly affected by SCD, and most who are affected come from lower socioeconomic strata. One study of children with SCD and their caregivers showed 61% of the caregivers had a high school diploma or equivalent as their highest level of education achieved,⁴² whereas approximately 28.2% of the U.S. population older than 25 claimed the same (an additional 14.2% claim some high school with no diploma).⁴³ Additionally, 50% of the SCD caregivers surveyed reported a yearly household income of \$20,000 or less.⁴² Similarly, a large study of Black SCD patients found that patients and their families had lower median income levels and higher numbers of unemployed or disabled caregivers compared with the U.S. Black population as a whole.⁴⁴

Race must enter into this conversation. Most individuals with SCD in the United States are African American. Racial disparities in the quality of health care have been documented extensively, most notably for many cancers,^{45,46} HIV/AIDS,⁴⁷ and cardiac disease.^{48,49} There are many causes for these disparities, but race is often an independent predictor for differential health care and outcomes⁴⁸⁻⁵⁰. The U.S. has a history of racism⁵¹ that may contribute to these types of racial disparities in health care, and funders and those who influence them may not be immune to racism. Racial bias may influence where funding goes, whether or not this possible influence is intentional, making it reasonable to consider the possibility that racism is a factor in the lack of development of new therapies for SCD.

Structural Violence and Sickle Cell Disease

Medical research funding is primarily delivered by industry, government, or philanthropic organizations. If the possibility of profit—be it political or financial—to the funder is not anticipated, then the funder is less likely to support that research. For instance, in the case of the pharmaceutical company, a project must either be profitable or generate a significant amount of public goodwill to be pursued.

In the case of foundational or non-governmental funding, an organization may be specifically founded to raise awareness and funding about a particular condition. These foundations primarily fund research related to this condition, which is the case for groups such as the CFF or SCDF. Other groups work on health-related issues but are not founded to focus on one particular condition, such as the Bill and Melinda Gates Foundation. A coordinated advocacy campaign strengthens appeals to these foundations for support and may influence public opinion. One example is the cancellation of funding for the proposed “Urun III” hydroelectric dam that was to begin building in Nepal in 1995 after intense advocacy efforts.⁵² We believe that such a campaign is less possible for a constituency that is on the wrong end of the socioeconomic spectrum.

Finally, government-sponsored research must be deemed important enough to the public welfare to fund the research. If a particular constituency is more vocal or well funded, it may

be able more effectively to promote research and gain the attention of additional funders. Public opinion⁵³ and advocacy⁵⁴ are historically important here as well and may greatly influence funding.

Because of the possible influences on funders of public opinion and advocacy⁵³⁻⁵⁵, the socioeconomic characteristics of those living with SCD may make funding for research on this condition less likely. Pharmaceutical companies may not make significant profits from a treatment targeted at SCD, as the afflicted individuals are relatively poor⁴² and have relatively high uninsured rates⁵⁶. As most pharmaceutical companies have a strong responsibility to their stockholders, pursuing a treatment that may not be profitable may not be feasible or desired. Because the SCD constituency has relatively less education and wealth, they likely also have less influence on those in power and of public opinion as delineated above. As a result non-profit organization and governmental funding for SCD is less likely.

The very structures by which research funding is awarded may push funding towards other conditions rather than to SCD. The constituency of SCD is largely poor, less educated, and less likely to be insured. This structure makes it less likely that those who decide funding will fund research devoted to this condition because doing so will not gain them profits (in the case of for-profit companies), will not gain them support among wealthy individuals (in the case of non-profit groups) and is not demanded by public opinion (as would influence any of the potential funders.)

In the introduction to this paper we noted that structural violence reflected how society's structures hurt individuals or groups. Individuals with SCD and their families are negatively affected by the systems that fund scientific research. We've outlined above how race, relative poverty and poor education combine with the conditions that influence whether or not research is funded to lead to insufficient advances in treatment options for those with SCD.

Ethical Considerations

These analyses are troubling as they suggest that drug development may be inadequate to meet the needs of suffering patients on account of structural violence. Applying a Rawlsian interpretation of egalitarianism highlights the moral concerns raised by the example of sickle cell disease and structural violence. John Rawls charges that ideally each person is to have an equal right to the most extensive scheme of basic liberties compatible with a similar scheme of liberties for others and that any social or economic inequalities that exist must be arranged to the benefit of the least advantaged members of society.⁵⁷ Rawls' vision of equality acknowledges that inequalities will exist, but requires society and institutions to allow only inequalities that redound to the benefit of those worst off in society.

As shown, the morbidity and mortality associated with SCD limit the opportunities that those with this condition might otherwise have, and it affects a population extremely low in socioeconomic status - those "worst off" in a Rawlsian analysis. It would appear that, according to a Rawlsian account of justice, there is a violation in the case of SCD in the US. What makes the case of Sickle Cell Disease notable in this analysis is that, as argued above,

structural violence is largely responsible for the lack of an effective treatment for sickle cell disease. Individuals with sickle cell disease are not afforded the opportunities that Rawls calls for because structural violence has limited those opportunities.

In order to address the concerns raised by a Rawlsian perspective, funding and support for SCD treatments needs to become a priority for our society, especially in comparison with other diseases of similar prevalence and clinical impact, as those with SCD are negatively affected but societal structures as noted above.

Acknowledging that inequalities exist to the detriment of those with SCD and their families begs the question whether there are solutions to ameliorating this injustice by addressing structural violence. Neglected tropical diseases such as helminth infections provide examples of how increased emphasis by public and private institutions alike can lead to increased attention being paid to previously neglected diseases. Research funding related to helminthic infections in 2007 was approximately 51 million US dollars. By 2009, this commitment had increased to 79 million US dollars.⁵⁸ One initiative that has the potential to make a difference is the National Institute of Health's "Therapeutics for Rare and Neglected Diseases" (TRND) program, established in 2009. This program allocated \$24 million in 2010 to help researchers and advocates partner to bring new therapeutic options to the point of being ready for human trials, one of the pilot studies involves SCD.⁵⁹

This however, is a small program being piloted by one governmental agency. Other governmental agencies such as the National Science Foundation and the US Agency for International Development in the U.S- and similar agencies in other developed countries - ought to allocate funding towards this type of research, at least to levels consistent with similar conditions, such as CF, especially in light of SCD's higher relative morbidity. It would seem a Rawlsian account of justice would demand as much. While these agencies may allow for some funding to target neglected diseases, formal programs such as TRND inform researchers of the possible funds available, allowing for long term planning.

Moreover, incentives could be created for non-governmental agencies in the form of matching public-private grant funding for research devoted to neglected diseases such as SCD. Pharmaceutical companies could be provided tax incentives for research directed at particular neglected diseases such as SCD. Finally, universities could seek out basic science and clinical researchers that focus on neglected conditions such as SCD as part of their social and academic missions. There are numerous possibilities to increase support for research that would likely improve the lives of those with SCD. Some may argue it is not the government's role to incentivize research in this way; however, we have already prioritized other areas in research for a variety of reasons. In the case of SCD, these programs would push for a more equitable share of research effort, especially in light of a Rawlsian analysis of the inequity.

Sheehan and Sheehan note that 'one central foundation of a just society is widely held to be an equal distribution of health outcomes across social classes and income groups.⁶⁰ Those suffering the effects of structural violence often are doubly disadvantaged when their already marginalized status extends further into basic goals such as access to health. As stated by

Beyrer *et al* “we continue to ignore neglected diseases to the detriment of public health in affected places, and our morals.”⁶¹ That we continue, as a society, to devote insufficient resources to SCD is poor public health practice, as ignoring an underserved segment of the population only worsens the state of that population’s overall health. As a function of this neglect, the health of a society as a whole is depressed. Unfortunately, this practices also speaks negatively to our moral conscience.

Summary

SCD is a disease that is prevalent in the U.S., largely in populations of African heritage and low socioeconomic status. Moreover, the literature referenced shows that SCD treatments, chiefly those related to SCD crisis are largely insufficient. This essay claims that the scope and impact of this disease is sufficiently broad affecting a population sufficiently disadvantaged to warrant more significant research (and research funding) particularly when the resources dedicated to CF, a devastating though less prevalent disease, are considered. We presented evidence to argue that the primary reason that SCD treatments have progressed insufficiently is related to structural violence as demonstrated through economic and racially motivated neglect. Finally the ethical implications of poor progression of SCD treatments due to structural violence in terms of justice theory were explored.

This essay has explored how this neglect is principally explained by structural violence in regards to SCD; a careful analysis would likely show structural violence as a root cause of the lack of interest shown to various other neglected diseases as well. For the efforts of those seeking to address neglected diseases to be truly effective, we must also tackle the issues of structural violence that have allowed these diseases to be ignored as long as they have.

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