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Original Research

A Punctuated Equilibrium Analysis of Amyloidosis (and Amyloid Related Diseases) in U.S. Policy Making

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Amyloidosis is a rare disease in which Amyloid protein accumulation leads to severe, systemic diseases affecting vital organs like the heart, kidneys, liver, and brain. The disease "Amyloidosis" has been discussed 451 times in the official United States Government Records (GovInfo.com) dating back to 1916. Baumgartner and Jones' (1993) Punctuated Equilibrium Theory (PET) helps explain policy change as a pattern of long stability interrupted by brief periods of significant shifts. Applying PET reveals four such punctuations in U.S. policymaking history. The most recent punctuation coincides with the first-ever introduction of two amyloidosis bills to Congress. The objective of the paper is to highlight the growth of amyloidosis and amyloid related diseases policy in the United States federal government. The narrative review incorporated all the United States Government Records that mentioned amyloidosis from GovInfo.com. There were four significant shifts in amyloidosis policy in the United States followed by a current state of stasis due to the restructuring of the NIH.

INTRODUCTION

Amyloid protein accumulation leads to severe, systemic diseases affecting vital organs like the nervous system, heart, kidneys, liver, and brain. Current treatment options are severely limited for amyloid related diseases. The complex, multi-organ nature of amyloidosis makes determining the fundamental mechanisms behind amyloid fibril formation, a key characteristic of the disease, exceptionally difficult.[1] The disease "Amyloidosis" has been discussed 451 times in the official United States Government Records (GovInfo.com) dating back to 1916.[2] There were 451 cases that included "Amyloidosis" – 1) Code of Federal Regulations (5), 2) Congressional Bills (13), 3) Congressional Committee Prints (5), 4) Congressional Documents (4), 5) Congressional Hearings (38), 6) Congressional Record (42), 7) Congressional Record (Bound Edition) (40), 8) Congressional Reports (27), 9) Congressional Serial Set (5), 10) Federal Register (93), 11) History of Bills (2), 12) Journal of the Senate (3), 13) Other Publications (140), and United States Courts Opinions (55).[2]

By using The Punctuated Equilibrium Theory (PET) developed by Baumgartner & Jones (1993), we can explain policy change which includes stability for a long period of time, followed by a short, punctuated, shift in policy.[3] The policy is usually triggered by either a major external event, a shift in the political environment, or public opinion. Punctuated Equilibrium Theory (PET) focuses on the mechanisms that lead to a policy change. Rather than gridlock and stability, Baumgartner & Jones stated that "we saw policy change as oftentimes disjoint, episodic, and not always predictable".[4] By building off the foundation of Bounded Rationality,[5] Sabatier (2007) stated that "political systems, like humans, cannot simultaneously consider all the issues that face them, so policy subsystems can be viewed as mechanisms that allow the political system to engage in parallel processing".[6] Sudden changes punctuate the balance of political power which is a balance between periods of stability and incrementalism. The framework can explain both stable years as well as dramatic changes.

According to Baumgartner and Jones (1991), policy venues, which is defined as "where images are in flux, one may also expect changes in institutional jurisdictions" can be used for strategy by public health actors. According to public health actors use the same strategies.[7] According to the National Collaborating Centre for Health Public Policy in Quebec, Canada, the "strategy consists of trying to act upon policy venues, either by limiting access to them or by gaining support for one's position in new policy venues".[8] In Israeli Health Policy, Feder-Bubis & Chinitz (2010) stated that the trajectory of change can be perceived in different ways by different policy actors, stakeholders, and elites. PET and specifically policy venues have been utilized by different policy actors, stakeholders, and elites in amyloidosis and amyloid related diseases.[9]

Throughout the 109 years in the United States Government that amyloidosis has been discussed or studied, there have been four dramatic changes in amyloidosis public policy. The first punctuations in amyloidosis policy occurred as the cigarette labeling and advertising congressional hearings were relevant in 1964 and 1965. The next punctuation occurred in 1978 with the establishment of the National Toxicology Program (NTP). The Department of Health, Ed-

ucation, and Welfare established the NTP and published its 100th technical report. Third, the Public Health Improvement Act of 2000 significantly boosted the NIH. This, coupled with basic research, public health awareness, clinical trial funding, and a growing understanding of amyloidosis' impact, expanded federal government involvement. Since 2000, 318 of the 451 total federal government cases were published. Finally, in 2020, the first two bills were presented to Congress involving amyloidosis, H.R.8652 - Dialysis-Related Amyloidosis Treatment Act of 2020 and Congressional bills H.R.8999 - Dialysis-Related Amyloidosis Treatment Act of 2024.[2]

AMYLOIDOSIS PUNCTUATIONS AND STASIS

FIRST PUNCTUATION – 1964 AND 1965 CIGARETTE LABELING AND ADVERTISING CONGRESSIONAL HEARINGS

A punctuation occurred as the cigarette labeling and advertising congressional hearings were relevant in 1964 and 1965. In PET, policy change from a crisis can occur such as the "1964 cigarette crisis" which refers to the landmark report, "Smoking and Health: Report of the Advisory Committee to the Surgeon General," that linked lung cancer and other health problems to cigarette smoke.[10] This led to a decline in smoking rates. For the first time in a congressional hearing, amyloidosis was referenced. The "House Hearing: Cigarette labeling and advertising: hearings before the Committee on Interstate and Foreign Commerce, House of Representatives, Eighty-eighth Congress, second session, on bills regulating the labeling and advertising of cigarettes and relating to health problems associated with smoking" called Dr. Milton B. Rosenblatt, Chest Physician, Chief, Medical Clinics, Metropolitan Hospital, New York to testify. In the hearing, Dr, Rosenblatt referenced his study on the "Clinical considerations and treatment of amyloidosis" in the U.S. Armed Forces Medical Journal (1951) as well as the "Amyloidosis and Amyloid Nephrosis" in the American Journal of Medical Sciences (1933).[11,12] The two hearings led to the Federal Cigarette Labeling and Advertising Act of 1965. Jones and Baumgartner realized that "policymaking both makes leaps and undergoes periods of near stasis as issues emerge on and recede from the public agenda"[6] In the case of amyloidosis, the subsystem was originally dominated by a single interest – Cigarette smoking and Cancer research, which is known as a policy monopoly. A successful policy monopoly occurs when a single image is widely accepted. According to Sabatier, "Policy monopolies are not invulnerable forever. A long-term view of U.S. policymaking reveals that policy monopolies can be constructed, and that they can collapse".[6] In the first punctuation, the cigarette smoking policy monopoly collapsed in 1965 after the Federal Cigarette Labeling and Advertising Act of 1965 was passed. For the first time, cigarette advertising was required to display health warnings.[13]

SECOND PUNCTUATION – ESTABLISHMENT OF THE NATIONAL TOXICOLOGY PROGRAM (NTP) IN 1978

From 1966 to 1977, there was a stasis period in amyloidosis research in the federal government. The next punctuation occurred in 1978 with the establishment of the National Toxicology Program (NTP). Congress and the public were concerned about the health effects of chemical agents in the environment. The Department of Health, Education, and Welfare established the NTP and published its 100th technical report. For example, in 1978, The National Institute of Health issued 48 Executive Agency Publications on "Chloropicrin (CAS 76-06-2) has been tested for cancer-causing activity with rats and mice in the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute."[14] For example, the "Summary of the Incidence of Non-Neoplastic Lesions in Female Mice Treated with Chloropicrin" study in the NCI Carcinogenesis Technical Report Series included amyloidosis in the 1) Spleen, 2) Digestive System, and 3) Kidney. The test included 1) Control (UNTR) 02-f041, Control (VEH) 02-F031, Low Dose 02-F044, and High Dose 02-F045.[14]

The NCI research on amyloidosis in animal models such as mice led to several studies on human patients. Kyle et. al. (1997) investigated different treatments for amyloidosis in a randomized, placebo-controlled, double-blind study of 55 patients. This included colchicine, melphalan, and prednisone.[15] In addition, Yi et. al. (1991) study using transgenic mice carrying human mutant transthyretin genes was underway to understand the mechanisms of amyloid deposition in familial amyloidotic polyneuropathy (FAP).[16]

THIRD PUNCTUATION – PUBLIC HEALTH IMPROVEMENT ACT OF 2000 – ADVANCEMENT OF THE NATIONAL INSTITUTE OF HEALTH

According to Gov Info, from 1979 to 1999, 43 cases included amyloidosis, which would be the next phase of stasis (Gov Info). Then, in 2000, the Public Health Improvement Act of 2000 was passed which focused on improving NIH operations including public health infrastructure such as focusing on infectious disease surveillance, bioterrorism preparedness, and strengthening public health capacities. While the bill did not specifically mention amyloidosis, it helped provide grants from the NIH to organizations that focused on cancer research, Alzheimer's, neurosciences, and kidney diseases. The NIH also received additional funding through the Children's Health Act. The NIH received the largest change in budget year-to-year from 1999 to 2003 since 1996 (1999 – 15.6%, 2000 – 17.8%, 2001 – 20.4%, 2002 – 23.3%, and 2003 – 27.2%).[17]

The combination of basic research, public health awareness, funding for clinical trials, and a growing understanding of amyloidosis' impact all contributed to the expansion of the federal government's involvement. According to GovInfo, since 2000, 318 of the 451 total federal government cases that mentioned amyloidosis were published. For the past 25 years, amyloidosis research in the federal government has been in a constant state of punctuation and gradualism. To put this in retrospect, Alzheimer's Disease had

an overall 20,295 cases published on GovInfo. Amyloidosis and amyloid related diseases are mentioned approximately 2% of the rate that Alzheimer's is mentioned. In addition, according to Ballreich et. al. (2021), Alzheimer and dementia funding increased the most of any diseases from 2008 to 2019, with approximately $1.8 billion.[18]

In addition, 36 of the cases include major advances in immunoglobulin light chain (AL) amyloidosis. According to Muchtar et. al. (2017), they had 1,551 newly diagnosed patients at Mayo Clinic, Rochester, Minnesota from 2000 to 2014 with a newly diagnosed AL amyloidosis. They stated that "The introduction of serum free light chain (sFLC) assays early in the millennium enabled the detection and quantification of the amyloidogenic light chain in the serum, which may be at a level below the detection sensitivity of serum protein electrophoresis and immunofixation".[19] For the past 40 years, the mortality rate for six months was approximately 40% at Mayo Clinic. However, they witnessed the six-month mortality rate decrease from 37% to 24% due to the availability of earlier diagnosis research and the increase in effective treatments available. The treatment options included the introduction of MDex and bortezomib-based regimens as the first line of therapy rather than melphalan and prednisone.[19] Their study was funded by an NIH NCA grant. The NIH Specialized Center for Research and Development grant focused on including bortezomib-based regimens in not only patients with amyloidosis but also myeloma and POEMS (Polyneuropathy, Organomegaly, Endocrinopathies, Mono-clonal protein, Skin changes).[19-21]

The advancements in treatment and diagnosis for AL amyloidosis also contributed to a six-month mortality decrease from 23% to 13% from 2010 to 2019 at the Boston University Amyloidosis Center.[22] They stated that during this timeframe, "Beyond treatments, standardized risk-stratification and treatment response assessment, owing to the advent of the serum-free light-chain assay and organ dysfunction biomarkers in the 2000s, contributed to a much-improved outlook for this rare disease".[22] Also, long-term survival has increased, where now 1 in 5 patients have longevity of 10 years.[22]

The trend in amyloidosis research was not only present in the United States government but also in England. In 1999, the National Amyloidosis Centre (NAC) was commissioned by the National Health Service. Pinney et. al. (2013) found that between 2000 and 2008 there was a rise in patients death certificates that were diagnosed with amyloidosis based on data from the NAC as well as the Office of National Statistics (ONS).[23] They stated that "This apparent rise may reflect an actual increase in disease incidence but could equally well be attributed to better awareness of the disease itself and/or existence of a national referral center as well as improved diagnostic techniques".[23]

The NIH also funded a study that found geographic disparities in reported U.S. amyloidosis mortality rates. From 1979 to 2015, The mortality rate for cardiac amyloidosis was higher in states with a greater proportion of black men, nearly doubling white men (12.36 per 1,000,000 vs. 6.20 per 1,000,000). Also, the overall male mortality rate was higher than that of female. Alexander et. al. (2018) stated that "The increased reported mortality over time and in proximity to amyloidosis centers more likely reflects an overall increase in disease diagnosis rather than increased lethality."[24] Amyloidosis is continuously being classified as a cause of heart failure, even if it is classified as a rare disease.[25] This NIH grant as well as others benefited from President Clinton's 1998 National Center on Minority Health and Health Disparities which provided a larger budget to pursue the disproportionate rates of diseases in minorities.[26-28]

FOURTH PUNCTUATION – H.R.8652 - DIALYSIS-RELATED AMYLOIDOSIS TREATMENT ACT OF 2020 AND CONGRESSIONAL BILLS H.R.8999 - DIALYSIS-RELATED AMYLOIDOSIS TREATMENT ACT OF 2024

On July 11th, 2024, the second congressional bill that specifically mentioned amyloidosis was introduced titled the H.R.8999 - Dialysis-Related Amyloidosis Treatment Act of 2024.[29] The first bill was introduced on October 23rd, 2020.[30] The bill aims to improve access to treatment for patients who suffer from amyloidosis (dialysis-related). The bill ensures that patients with dialysis-related amyloidosis will receive coverage and payment under Medicare. This includes all FDA-approved treatments for dialysis-related amyloidosis. The bill would amend Title XVIII of the Social Security Act. As of December 17th, 2024, the bill was referred to the Subcommittee on Health.[30]

Another component of PET includes the venue change.[6] Amyloidosis was a highly technical topic in which only physicians would be the technical individuals that would present their findings as we witnessed with the 1964 and 1965 Cigarette Labeling and Advertising Congressional Hearings. However, as amyloidosis has expanded, all levels of government have become involved, including the 13 categories from GovInfo and specifically in this case brought to the House of Representatives floor by congressional representatives. The 13 categories included 1) Code of Federal Regulations (5), 2) Congressional Bills (13), 3) Congressional Committee Prints (5), 4) Congressional Documents (4), 5) Congressional Hearings (38), 6) Congressional Record (42), 7) Congressional Record (Bound Edition) (40), 8) Congressional Reports (27), 9) Congressional Serial Set (5), 10) Federal Register (93), 11) History of Bills (2), 12) Journal of the Senate (3), 13) Other Publications (140), and United States Courts Opinions (55).[2]

CONCLUSION AND FUTURE DIRECTION

All four periods of stasis and punctuations met Baumgartner and Jones's (1993) Punctuated Equilibria in U.S. Policy Making. First, policymaking makes leaps and undergoes periods of stasis based on issues emerging and receding from the public agenda.[31] Second, American political institutions exacerbate the punctuated equilibria for amyloidosis including the Legislative Branch (Five bills mentioned), Executive Branch (National Health Institute and National Cancer Institute), and Judicial Branch (55 United States

Supreme Court Opinions). Finally, policy images played a crucial role in expanding issues such as Cancer from Cigarettes in 1964, Chemicals from the Environment in 1978, strengthening public health infrastructure at the federal, state, and local levels and bioterrorism preparedness in 2000. All these policy images as well as venue change helped bring amyloidosis research to the forefront in the current punctuations which brought H.R.8652 - Dialysis-Related Amyloidosis Treatment Act of 2020 and Congressional bills H.R.8999 - Dialysis-Related Amyloidosis Treatment Act of 2024 to the congressional floor. We are moving toward a stage of stasis due to a lack of movement of the bill H.R. 8999 on the congressional floor since the new administration started in January as well as the restructuring of the NIH staff and funding.[32]

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