History of Pharmacy SIG

Pharmacy Chronicles: Past, Present, and Future

Welcome Message from the Chair, History of Pharmacy Special Interest Group

June 2020, three months into pandemic shutdown, was an interesting time to step into a new role as the Director of Academic Programs and Student Services for the Ohio State University's College of Pharmacy. I had spent the previous ten years deeply embedded in the world of teacher education, first at Ohio State, and then as the Director of Teacher Education for the State of Ohio. Prior to that, I had worked in curriculum development and student services for Arts and Sciences. It was all a matter of timing when a former employee of mine reached out to let me know he was leaving his position so his spouse could take a dream job across the country, and he knew I would love the work he was stepping away from, and he was not wrong.

I have always been someone actively involved in national associations, but finding that new home during shutdown, was a challenge, and I was unsure if I would find a place as a staff member within AACP. Discovering this SIG was the spark – my doctoral research was the history of higher education, and I was excited to feed my passion for all things history with a new content area for me: history of pharmacy. While my pharmacy content expertise is minimal, it is growing thanks to this group. I know there are many others like me, professionals without a pharmacy background, or faculty who simply have a love of history. Some of you may simply be helping your programs to meet the accreditation standards and are seeking resources. What I have come to understand over the past few years is that there are opportunities for all of the 170+ members of our SIG, it's simply a matter of saying yes to the many calls for volunteers!

This summer's annual meeting provided a wonderful space for us to engage as SIG members. Michael Hegener and Essie Samuel hosted an exciting session: "Making History Innovative, Using Pharmacy History Activities to Support Content in a Variety of Courses. Our networking session had 20+ attendees who provided thoughts on what they would like to see this year. And our AIHP partners hosted a robust discussion about how we would like to engage with them, which has led to many discussions about how to help AACP members be prepared to publish.

Our Executive Committee has hit the ground running with setting our strategic priorities for the next three years while also focusing on goals for this year. I am truly excited about the energy they are bringing, the dedication to increasing committee participation, and setting the groundwork for becoming a go-to resource for all things History of Pharmacy for AACP members. No matter whether you are deeply embedded in work in the history of pharmacy, or call yourself a hobbyist, we hope you will join us this year!

Sincerely,
Jessica Mercerhill SIG Chair

INSIDE THIS ISSUE:

Meet the Editors

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Thank you ...
The Editors would like to thank the volunteers who performed the peer reviews and editing for this issue.

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Message from the Editors

Welcome

WELCOME! We are pleased to present the 17th issue in our 11th year of publishing, of the History of Pharmacy SIG Newsletter *Pharmacy Chronicles: Past, Present, and Future*. This is second issue for this year, and our fifth year of providing two issues per year thanks to the interest of our readers and to our intrepid authors who provide us with outstanding articles. A big Thank You to our peer reviewers who respond quickly and with constructive comments to the authors, resulting in a higher quality publication. We always welcome volunteers to be peer reviewers; we appreciate your efforts and the burden is light.

Of course, our peer-reviewers must have something to read, so we also gratefully acknowledge the authors who have taken the time to provide insightful and interesting stories to better illuminate our professional history. In that vein, we encourage our readers to enlist the aid of your students to add to our pages. A number of our articles have both teacher and student authors and they do a great job! Also, as many of our readers are teachers of pharmacy in so many disciplines, please take a moment as you organize your courses and lectures to incorporate some historical facts or context for drugs

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ANNOUNCEMENTS

Editor's Notes, continued from pg. 2.

or diseases. One never knows where that spirit of inspiration will well up.

Once again, we have very diverse topics in this edition ranging from the Boston Smallpox epidemic of 1721 and the inoculation controversies of the time to the history of levothyroxine. Also, please don't miss the brief article highlighting the oral history project of the U.S. Public Health Service Chief Pharmacist Officers from 1987 to 2022, and then read the full transcripts available on the AIHP website. The descriptions of the diversity of backgrounds and experiences of these officers is a delight to read as well as a picture of the life and times of the period.

Please note that we welcome a short, newsy piece of trivia or a full article for peer review (1500-2000 words). Pictures are always good! To volunteer, contribute as author or peer reviewer or just have a question or suggestion, please feel free to contact either Megan Undeberg or Bernie Olin. We are always happy to hear from you.

—Bernie Olin, PharmD.,
Auburn University,
Harrison College of Pharmacy

RECOGNIZE YOUR STUDENTS FOR THEIR ACTIVITIES RELATING TO THE HISTORY OF PHARMACY!

The American Institute of the History of Pharmacy offers certificates to students to recognize their achievements in the area of History of Pharmacy. Nominate deserving students at the link below. The certificates could be sent directly to the students or to the schools for presentation at an awards ceremony.

Link: #AIHP/ Student recognition certificate

History of Galantamine and Acetylcholinesterase Inhibitors for Alzheimer's

By: Caylen Wouters, Brianna Smith, Westley Schlundt, Student Pharmacists 2025 and

Bernie R. Olin, Pharm.D.

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Discovery of galantamine and its clinical development

Galantamine [(4aS,6R,8aS)- 5,6,9,10,11,12-hexahydro-3-methoxy11-methyl-4aH-[1]benzofuro[3a,3,2-ef][2] benzazepin-6-ol] is a benzazepine that reversibly and competitively inhibits the acetylcholinesterase enzyme.[1,2] Galantamine (aka, galanthamine) is commonly derived and named from the *Galanthus* species (widely known as snowdrops) and other Amaryllidaceae plants.[1] The *Galanthus* species are native to many areas of Europe including Bulgaria, Turkey, and the Caucasus mountains.[3] The possible earliest mention of the use of *Galanthus* was theorized by two neurologists, Andreas Plaitakis and Roger C. Duvoisin, in 1983.[4] They hypothesized that Homer's "moly" might have been the snowdrop, *Galanthus nivalis,* based on its description within the poem, Odyssey, and its use by Odysseus as an antidote against the enchantress Circe's poisonous drugs.[4] It is thought that Circe used centrally-acting anticholinergic agents to induce amnesia and delusion.[4] Based on this, the two neurologists are convinced this may be the oldest recorded use of an acetylcholinesterase inhibitor.[4] In the 1950's there were unconfirmed reports from a Bulgarian pharmacologist that he observed native people using wild snowdrops to relieve nerve pain by rubbing it onto their foreheads.[3] In 1965, a London pharmacognosist, E.J. Shellard attended a presentation where a fellow pharmacognosist from Russia recounted observing peasant women in the Caucasian mountains using Caucasian snowdrops (Galanthus woronowii).[3] It was reported that it was given to young children who developed signs and symptoms of what is now known as poliomyelitis.[3] The children who received this extract of the snowdrop bulb completely recovered without showing any signs of paralysis.[3] These secondhand reports are only one of few available recordings of the use of snowdrops before the development of the drug, galantamine.[3]

The first set of investigations done on galantamine were conducted in Bulgaria and Russia during the Cold War (1947-1989).[3] In 1951, Russian pharmacologist Mashkovsky partnered with Kruglikova-Lvova to study the use of galantamine from the *Galanthus woronowii*.[3,5] They used striated muscles from frogs and smooth muscles from rabbits and guinea pigs to study its acetylcholinesterase inhibition and its antagonizing effects on curare (a plant toxin that commonly causes paralysis).[3,5] In 1952, the Russian chemists Proskurnina and Yakovleva were the first to extract galantamine from Galanthus woronowii and establish the chemical structure as an alkaloid with a tertiary nitrogen.[3] In 1957, Bulgarian scientist Bubeva-Ivanova was the first to extract this same alkaloid from the leaves of the plant *Galanthus nivalis*.[3] Around the same time, other sources of galantamine were identified such as the Narcissus species and Leucojum aestivum, with Leucojum aestivum emerging as the primary source of galantamine in Eastern Europe.[3] It was the research of D. Paskov (Mashlovsky's mentee) in 1957 that the cholinesterase-inhibiting properties were demonstrated and published.[3] The indication for galantamine was established in the 1950s for poliomyelitis in Eastern Europeans as a result of the data that galantamine enhances nerve impulse transmissions at the synapse.[3] It was sold under the brand name of "Nivalin" in 1958 as an injection and as a tablet starting in 1984.[3] From the studies of Nesterenko and Iliyuchenok, it was found in 1965 that galantamine can cross the blood-brain barrier, being a tertiary ammonium base.[5] Galantamine was then characterized as a reversible inhibitor of mixed type with predominantly competitive acetylcholinesterase inhibition in 1974 by Vasilenko and Tonkopy.[5] It wasn't until the 1990's when there was research that showed galantamine improving memory dysfunction in mice that spurred the idea that galantamine could be used for Alzheimer's disease (AD).[6] In 1996, galantamine was licensed for the use of AD in Iceland, Ireland, Sweden, and the United Kingdom.[1] Galantamine hydrobromide was approved by the U.S. Food and Drug Administration (FDA) in 2001 under the name "Reminyl." It was later changed to "Razadyne" in 2005 and is now considered a first-line therapy for treating Alzheimer's disease.[1,2,7]

AD was originally described in 1907 by a German psychiatrist, Alois Alzheimer.[3] It was not until 1977 when scientist P. White and others published an article in *The Lancet* about the significant decrease in acetylcholine and muscarinic binding receptors in the frontal

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Triumphs and Tributes:

The Extraordinary Journey of Nobel Laureate Alfred Goodman Gilman

By Martin Patrick, PharmD, MS, MSHA, Touro College of Pharmacy Class of 2023;

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As student pharmacists, we sometimes overlook the significance of the names behind some of the most widely used resources, such as Dipiro's, Goldfrank's, Harrison's, and Goodman and Gilman's. One of the most respected publications in the field of pharmacology, Goodman and Gilman's *The Pharmacological Basis of Therapeutics* came to fruition thanks to Alfred Goodman Gilman Sr, a distinguished pharmacologist who co-wrote the first edition of Goodman and Gilman published in 1941.[1,2] Later, his son Alfred Goodman Gilman Jr., more famously known as "Al" in the scientific community, continued his father's legacy and may have even surpassed him in fame. Al was introduced to the scientific community by accompanying his father on trips to laboratories at Columbia University and Albert Einstein College of Medicine.[2] He edited several editions of Goodman and Gilman's, alongside his father.[1]

Alfred, as he put it, was born with a "scientific silver spoon" in his mouth on July 1, 1941, in New Haven, Connecticut.[2] He began his career by earning his BS in biochemistry from Yale University, followed by an MD-PhD from Case Western Reserve University in Cleveland, Ohio.[3] While conducting research, he developed a keen interest in the cellular signaling pathway. As a postdoctoral fellow, he delved into this pathway to gain a deeper understanding. It was during this time that he made a groundbreaking discovery—the G-protein—which ultimately earned him the Nobel Prize for Physiology or Medicine in 1994. Along his journey, he collaborated with American biochemist Martin Rodbell, who conducted similar research and shared the Nobel Prize for his significant discovery concerning the G-protein—a demonstration of its transducer function.[4] This transducer function plays a pivotal role in the signal transduction of cellular signaling.

In his Nobel Prize acceptance speech, Al described how the complexity of the human body and the cells within ultimately boils down to expression of only a few individualized components.[4] His and Dr. Rodbell's research illuminated how cells in the body receive signals from external stimuli such as light and odor and relay them internally to generate responses. Furthermore, signals can also transmit through the body via hormones produced by the body itself.[5] The G-protein discovery elucidated how these molecular switches inside cells transmit signals from outside the cell to its interior. Their discovery remains relevant and has led to numerous new therapeutic approaches for conditions like heart disease, pain, inflammation, Alzheimer's disease, and various cancers.[6] Notably, G-protein-coupled receptors (GPCRs) represent approximately 17% of all protein targets for approved drugs.[6]

Al was ahead of his time; with today's technology, he could have made even more significant contributions. Many diseases, such as cancer, involve genes being switched on, leading to metastasis—research areas where he could have made a profound impact. Throughout his life, he made numerous contributions. He served as Chairman of Pharmacology at UT Southwestern Medical Center in Dallas, TX, for over two decades. Additionally, he held the position of Chief Scientific Officer of the Cancer Prevention and Research Institute of Texas (CPRIT) until 2012. In these roles, he championed scientific integrity and advocated for rigorous science education.[7] He authored a column on behalf of a group of scientists, urging the Texas Board of Education to resist attempts to de-emphasize the teaching of evolution.[7] Importantly, he expanded the integrity of scientific research by recruiting eminent scientists from around the country to establish a review process that ensured the highest standards in evaluating research proposals. He also led the National Institutes of Health (NIH) Alliance for Signal Transduction, which united leading investigators from the country's top research institutions in a collaborative effort to define molecular pathways controlling the most critical cellular processes.[7]

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U.S. Public Health Service Chief Pharmacist Officers Oral History Project

Bernie R. Olin, Pharm.D., Editor

There is a treasure residing on the website of the American Institute of the History of Pharmacy (AIHP), among many others there. Specifically, it is the "U.S. Public Health Service Chief Pharmacist Officers Oral History Project."

Based on their belief that the rich history of U.S. Public Health Service and its pharmacists deserved more prominence, RADM Richard J. Bertin and RADM Richard M. Church (both retired Chief Pharmacist Officers (CPOs)) have provided a more complete record of the careers of other CPOs through oral history. They teamed with William A. Zellmer, a pharmacist with a rich publishing history and experience in conducting oral history interviews. The three of them approached and organized an oral history project that documented the development and significant contributions of eight former CPOs, each serving a term of four years, from 1987 to 2022. They are:

· Rear Admiral (Retired) Pamela Salas Schweitzer
RADM Schweitzer served as CPO between 2014 and 2018.

· Rear Admiral (Retired) Scott F. Giberson
RADM Giberson served as CPO between 2010 and 2014.

· Rear Admiral (Retired) Robert E. Pittman
RADM Pittman served as CPO between 2006 and 2010.

· Rear Admiral (Retired) Richard S. Walling
RADM Walling served as CPO between 2001 and 2005.

· Rear Admiral (Retired) Fred G. Paavola
RADM Paavola served as CPO between 1996 and 2000.

· Rear Admiral (Retired) Richard J. Bertin
RADM Bertin served as CPO between 1992 and 1996.

· Rear Admiral (Retired) Richard M. Church
RADM Church served as CPO between 1987 and 1992

In total, the CPO interviews constitute a substantial narrative about the public service of PHS pharmacists, through their day-to-day work in various federal agencies or when deployed by the government to help respond to national or global health emergencies. The eight interviewees discuss how they started in pharmacy (it often was not their first choice and they were rarely influenced by a pharmacist family member), how their pharmacy education equipped them for impactful leadership in various facets of public health, both domestically and internationally and they present important insights on the personal qualities and leadership approaches that contributed to their success.

Although each CPO provides a narrative of their personal journey, collectively they provide a wonderful insight into the development of clinical pharmacy that was beginning to blossom during this time. Some of the lessons/advice that are woven in the stories include:

"Networking is very important."

Each CPO could name influential mentors in their careers that helped guide them on their journey.

"Don't burn bridges on your journey."

"Take opportunities as they are presented, even outside your comfort zone."

"Flexibility."

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US Public Health Service CPO Oral History Project . . .

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"Preparation is important."
(e.g. additional training such as MPH, MS, various credentials)

"Work/life balance."

Most recognized that this was a struggle, but there was also awesome responsibility.

Transcripts of oral history interviews of these pharmacy leaders are accessible at this website: https://aihp.org/collections/u-s-public-health-service-commissioned-corps-oral-history-project/

Knowing how creative the teachers of pharmacy history are, they will not lack for ideas on how to use the PHS oral-history transcripts in their instruction. The transcripts may also have some utility in general orientations to the profession of pharmacy; in efforts to advise student pharmacists on career opportunities; and as source-material for leadership development discussions.

Here are some specific ideas provided by the authors, Dick Church, Dick Bertin, and Bill Zellmer. These can be used by students/residents to discuss lessons that apply to current profession-wide efforts to advance pharmacy.

- Identify important ways in which the US Public Health Service has helped the pharmacy profession as a whole advance over recent decades.
- Identify the unique characteristics of the pharmacy-practice environment in the US Public Health Service that help foster advancement of the pharmacist's role in patient care.
- Analyze the leadership characteristics that allowed these pharmacists to have outstanding careers in the US Public Health Service.
- Discuss how pharmacy-practice advances in the US Public Health Service have complemented broader initiatives to elevate the profession over recent decades.
- Identify examples of being prepared to accept/pursue unanticipated opportunities that arise in a pharmacy career.
- Discuss ways in which a pharmacy education can be excellent preparation for success in broad areas of public health.
- Identify examples of the role of mentorship in career development.
- Identify the unique career opportunities for pharmacists in the US Public Health Service.
- Discuss how pharmacists in the Indian Health Service helped the profession as a whole build its capacity for patient counseling. *(specific to the Church interview)*
- Identify common challenges that women pharmacists have faced in pursuing a leadership role in health care. *(specific to the Schweitzer interview)*

History of Pharmacy SIG

NEW!

See Articles that catch your eye from the Spring 2024 and Fall/Winter 2024 Issues?

Watch for 'Submission of the Year" nominations in Spring 2025!

History of Levothyroxine

By Hannah Best, Student Pharmacy 2026, Marilyn N. Bulloch, PharmD, BCPS, FCCM, SP, and Bernie Olin, PharmD
Auburn University Harrison College of Pharmacy

Hypothyroidism is a condition that affects nearly 5 out of 100 Americans ages 12 years and older.[1] Hypothyroidism can be diagnosed with laboratory tests and imaging; treatment is then based on these results. Levothyroxine is the most common treatment for this condition and has become one of the most commonly used medications in the United States today with about 7% of the population estimated to have an active prescription.[2] However, the discovery of levothyroxine began long before those technologies were developed.

The first documented case of the use of thyroid hormone for the treatment of hypothyroidism, which at the time was referred to as myxoedema, was in 1891. George Murray was a professor of systematic medicine at Victoria University and a physician to the Manchester Royal Infirmary. Murray believed that myxedema was connected to the thyroid gland and suggested using a healthy thyroid gland to treat the condition. At the Northumberland and Durham Medical Society meeting in February 1891 in Britain, Murray presented a case of a 46-year-old female with symptoms of slowed speech, enlarged hands and feet, and difficulty carrying on ordinary tasks. Murray believed that he could treat her with thyroid gland and presented his findings and ideas for treatment to colleagues at the conference.[3] In April 1891, the thyroid gland was extracted from a freshly killed sheep and thyroid extract was prepared. The patient then began receiving 1.5 mL of thyroid extract under the skin twice weekly.[3,4] She had significant symptom improvement including decreased swelling of the eyelids and face, normalization of menstrual cycles, increased energy, and decreased sensitivity to cold.[3] Following Murray's first publications about his success with thyroid injection, Hector Mackenzie, a London physician, argued that the subcutaneous injection had many disadvantages, including swelling or infection at the injection site, and suggested that thyroid be given orally with a "little brandy."[4] Mackenzie reported that he had treated patients successfully with oral thyroid extract. After reading Mackenzie's reports of success in *The British Medical Journal* in 1892, Murray began giving his patient thyroid extract orally as well.[4] She remained on the thyroid extract for 28 years before she died of cardiac failure in 1919. Following her death, Murray published his final results in *The British Medical Journal* in 1920.[3] Murray calculated that in the 28 years the patient was receiving thyroid extract, she consumed around 5 liters of thyroid extract derived from around 870 sheep.[3,4]

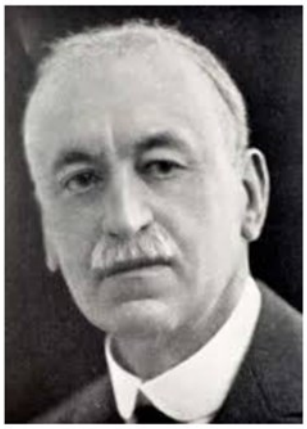

Figure 1: George Murray

Initially, thyroid extract taken directly from an animal thyroid gland was the only formulation used for treatment of hypothyroidism. Thyroxine was not isolated until 1914 by Edward Kendall.[4,5] Kendall named the compound thyroxin because he believed it was an indole derivative.[5] The chemical structure was determined by Charles Harington in 1926.[4,5] Harington renamed the compound thyroxine upon discovering that it was a tyrosine rather than an indole.[5] Thyroxine (T4) was then synthesized in 1927 by Harington.[4,5] Murray Lyon then tested this synthesized T4 in two patients and its effect was similar to what had been seen with thyroid extract. Soon after thyroxine was first synthesized, it became commercially available likely prior to a legal requirement for FDA approval in the United States. It was, however, rarely used because it was expensive and dried thyroid preparations were considered to be equally effective.[5] Doubt among clinicians that T4 was the circulating hormone in the body also led to hesitation in its use. This doubt stemmed from observing a long latent period of action when injected into animals and that T4 was inactive in most *in vitro* systems. Harington evaluated this hypothesis. In 1944, he proposed that T4 was the circulating hormone in the body.[5]

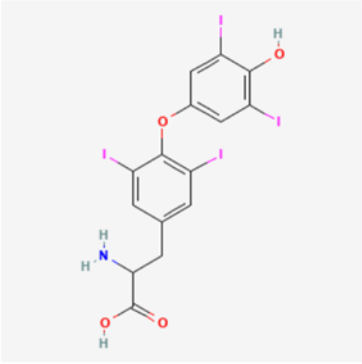

Figure 2: Chemical structure of thyroxine

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The Boston Smallpox Epidemic of 1721 and Controversy Surrounding Inoculation Practices

By Bailey Kincaid, PharmD Candidate and Michael Hegener, PharmD
University of Cincinnati James L. Winkle College of Pharmacy

While Edward Jenner (1749 – 1823), an 18th century British physician, is often coined the father of immunology, and creator of the first vaccine, practice in scientific techniques that resulted in immunity from disease predate him. In the fold of a smallpox epidemic afflicting Boston in 1721, Cotton Mather (1663 – 1728), a prominent New England puritan began promoting the use of a technique he learned about to prevent severe illness – inoculation.[1] Although Jenner's later work earned widespread recognition, the pioneering efforts of figures like Mather often go overlooked, perhaps illustrating a quote from Francis Galton (1822 – 1911): "In science credit goes to the man who convinces the world, not the man to whom the idea first occurs."[2]

The actual origin of the variola virus, which causes smallpox, is still a mystery with the first written account in records from 4th century CE China.[3] One of the earliest suspected cases comes from the mummified head of the Egyptian pharaoh Ramses V, who died in approximately 1160 BC from an acute infection. He was found with lesions characteristic of smallpox leading experts to consider it being his cause of death.[4] Smallpox has been attributed to many historical accounts of infections with symptoms of full body rash, pus-filled papules, painful scabs, permanent disfiguration, and death. With 25-55 million smallpox related deaths reported from 1520 and onward, smallpox proves to be one of the most fatal infections in history.[5] That is until variolation, a novel approach for preventing smallpox infections altogether, was discovered.

Variolation originated as the practice of taking a sample from a person infected with smallpox (pus, scab, or fluid) and inserting it into a healthy person's nose, often via use of a pipe. This traditional Chinese medicine practice for smallpox inoculation is believed to be of Taoist or Buddhist origin starting in roughly 900 AD. Very little written evidence is available to validate this claim or how the Chinese developed this practice, with many believing it was concealed as family trade secrets. One of the earliest written accounts of this unheard-of prevention technique was found by author Joseph Needham in a book published by Wan Chüan in 1727, *Tou Chen Shih I* Hsin *Fa*.[6] Once the smallpox sample was administered to the healthy patient wishing to be protected, they would experience smallpox-like symptoms, though typically in a milder state. A small portion of people would typically not survive though, but many speculated it being due a natural infection prior to administration. Once the mild infection passed, the patient was considered immune to smallpox with about 1 out of 10 patients experiencing complications (see fig. 1). This is much lower than the approximately 30% mortality rate from smallpox infection.[7-8]

Introduction of variolation practices to the western world can be attributed to Lady Mary Wortley Montague, the wife of the British ambassador to Constantinople in the early 18th century. Montague's letters detail her fascination with smallpox variolation commonly performed in Turkey, where it was an engraftment procedure rather than administered nasally.[9] A small incision would be made on a healthy individual's arm and a scab or pus from an infected person would be placed in the wound. While abroad, she had her son inoculated, then her daughter once back in England. She created a vogue state for Europeans, especially British aristocrats, to have inoculations performed on them and their family. While some became enlightened to this preventative measure, the colonies in America were continuing to suffer from disease; notably the 1721 outbreak of smallpox in Boston, Massachusetts.[10]Outbreaks of smallpox were common in colonial America, with one of the deadliest occurring in Boston between 1677-1678 with the death of 150 people in the first month alone. Those in the colony often regarded these epidemics as "divine intervention" for the sins of those afflicted. The public health response was almost identical to measures taken during the great plague of London: the mass exodus of the healthy and the imprisonment of the ill in their homes. The infected homes would be guarded by watchmen and a

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History of Levothyroxine…

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Further evidence to support that T4 was a circulating hormone came about in 1948 when Alvin Taurog and Israel Lyon Chaikoff found evidence that organic iodine in the circulation was irreversibly bound to T4. The use of radioactive iodine made it possible to demonstrate that the majority of protein bound iodine did contain T4. Even with new evidence and thyroxine becoming more economical in 1949, the use of these thyroxine tablets was not readily adopted. Despite this, T4 tablets were included in the British Pharmacopoeia in 1958. Most physicians at the time, however, were satisfied with the efficacy of desiccated thyroid and saw no need to switch to a new alternative.[5]

Triiodothyronine (T3) was identified in the early 1950s by Jack Gross and Rosalind Pitt-Rivers. This discovery was made at the National Institute for Medical Research in London where Charles Harington was the Director. An unknown substance was identified in thyroid extract in the plasma as well. T3 was then synthesized from 3,5-diiodothyronine and compared to the unknown compound. It was found to be chromatographically indistinguishable from the unknown compound. Finally, the compound was isolated from ox tissue and confirmed to be the same as the synthetic compound. T3 was determined to be three times more potent in rats than T4 which led to the belief that it was the active form of T4.[5]

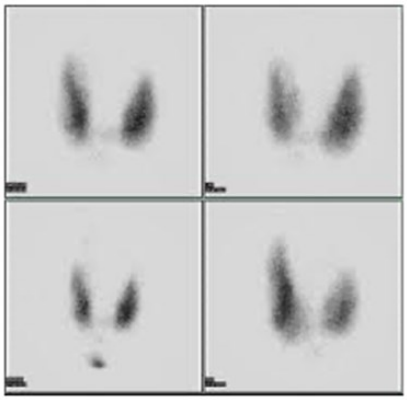

Figure 3: Radioactive iodine uptake test

Following this finding, some physicians were concerned that the use of L-thyroxine alone would result in a deficiency of T3. The discovery of the conversion of T4 to T3 in peripheral tissues helped to ease this concern.[6] In 1970, Lewis Braverman used highly sensitive TH displacement technology to demonstrate the conversion of T4 to T3 in patients who lacked a thyroid gland. Sterling also demonstrated this conversion in euthyroid humans within the same year. The development of radioimmunoassay for measurement of T3 and T4 provided an even greater push for the adoption of T4 as a first line option.[5] Desiccated thyroid was found to have a peak in T3 two to five hours after administration that led to toxicity in some patients. Single doses of L-thyroxine resulted in stable blood levels of T4 and T3 throughout the day due to the conversion of T4 to T3 at a steady rate.[6] A clinical trial conducted in 1970 also found that patients receiving a combination of T4 and T3 experienced more adverse effects including palpitations, nervousness, and perspiration. The trial concluded that monotherapy with thyroxine had advantages over the use of a combination therapy.[7] The combination of all these discoveries led to a greater shift from desiccated thyroid to L-thyroxine monotherapy.[6]

Levothyroxine officially became available in the United States in 1962 after following the determination that sodium L-thyroxine form was much better absorbed than the free acid thyroxine. However, the U.S. Food and Drug Administration (FDA) did initially require a New Drug Application (NDA) because it was considered a "new" drug. Adverse Drug Experience Reports eventually revealed problems with potency, stability, and consistency among different levothyroxine products.[8] On August 14, 1997 the FDA announced that levothyroxine products were, in fact, "new" drugs and needed to submit NDAs.[8,9] Levothyroxine was deemed medically necessary. Therefore, the FDA allowed three years for manufacturers to obtain new drug approval.[9] Despite this mandate by the FDA, Synthroid® received FDA approval in July of 2002.[10]

Many concerns were raised by the American Thyroid Association (ATA) following the new approvals of levothyroxine products. This led to recommendations by the ATA in December 2004 that patients remain on the same generic product throughout the duration of therapy rather than interchanging different generics. It was even recommended to check TSH levels more frequently if a change in levothyroxine product was made due to concerns about variability in bioavailability of the products.[8] In an effort to address these concerns, the FDA issued a letter in 2007 requiring all NDA holders to change the specifications for their products so that all levothyroxine sodium products met a 95% to 105% potency specification throughout their labeled shelf-lives.[11] The ATA recommended levothyroxine as the drug of choice for hypothyroidism as opposed to liothyronine or desiccated thyroid products. However, they chose to recommend against switching between different generic levothyroxine products when the 2014 Guidelines for the Treatment of Hypothyroidism were published.[12,13] Subsequently, generic levothyroxine has been less commonly prescribed despite the FDA indicating that generic levothyroxine is bioequivalent to the brand name preparations.[13,14] In the 2014 Guidelines for the Treatment of Hypothyroidism, the ATA states that there was concern particularly in frail patients, those with thyroid cancer, and pediatrics. The guidelines also indicate a need for investigation comparing various generics to each other and comparing brand name products to generic.[12] A trial was published in 2022 investigating this particular issue. This trial by Jonklaas J et al. evaluated whether there were clinically significant differences seen among different generic products. The participants were divided into two groups with one group remaining on the same generic product throughout the study and the other group changing between generics. No clinically significant differences were seen in TSH

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red flag would be placed that stated "God have mercy on this house". Quarantine and isolation were the only effective options in the American colonies at the time, that is, until a particular local epidemic of smallpox would change this. On April 22, 1721, the British naval ship, HMS *Seahorse*, which had two seamen afflicted with smallpox onboard, docked at Long Wharf in Boston, bringing smallpox ashore. Within a few months, there was a rapid increase in cases and public panic ensued. Fortunately, one man considered an "anti-hero" by today's historians had devised a plan for such a situation a few years prior.[11]

The man was Rev. Cotton Mather, a well-known Puritan minister, who prior to the 1721 Boston outbreak was one of the key figures involved in the Salem witch trials. Clergy men of the time were considered some of the most educated citizens, with some possessing varying levels of medicinal knowledge. Mather had graduated from Harvard College at 15 years old and briefly considered a career as a physician. His interest in the sciences, or "natural philosophy," was demonstrated by his massive library of 444 books and pamphlets on varying scientific topics. Mather first learned of variolation practices in 1707 from his African slave, Onesimus, who when asked if had ever had smallpox, replied, "Both, yes, and no." He described the procedure common to his tribe, the Guaramantee, and displayed his scar as proof. This novel technique was reinforced to Mather in 1716 after reading the letters of an unnamed Turkish physician in the Royal Society of London's *Philosophical Transactions* journal. The letters described the same variolation techniques observed by Lady Montague in 1721.[11]At the dawn of this new dilemma in Boston, Mather wrote in his diary, "the grievous calamity of the smallpox has now entered the town. The practice of conveying and suffering the smallpox by inoculation has never been used in America, nor indeed in our nation. But how many lives might be saved by it, if it were practiced?" On June 6, 1721 Mather wrote to the physicians of Boston, presented the evidence he gathered for the benefits of small-pox inoculation, and asked for their help in implementing it. Unsurprisingly, he received no replies, even after a second attempt on June 23. Mather then reached out to Dr. Zabdiel Boylston, a well-known surgeon and apothecary with a reputation for performing risky procedures. With confidence in the evidence provided by Rev. Mather, Boylston inoculated his six-year-old son Thomas, his 36-year-old African slave, Jack, and Jack's two-year-old son. After a tense week of waiting for their symptoms to subside after inoculation, Boylston was relieved to see all three return to normal health. After this success, news of the experiment had begun to circulate in the community with mixed feelings.[11]

The immediate response was furious astonishment. Boylston was bombarded with insults and abuse while in public, and outcries for him to be hanged for attempted murder persisted. His attempt to quell the communities clammer failed after his notice in the *Boston Gazette* said he planned to inoculate others. After he ignored two orders to appear before authorities, a public meeting was held on July 21, 1721, consisting of Boston's physicians, justices of the peace, and an audience of concerned citizens. Erroneous tales and false dangers of inoculation were presented, and condemnation of Boylston was clear, even after the group refused an invitation by him to see his patients' progress. This sparked a furious printed battle between both sides. Opponents such as William Douglass, a formally trained medical professional and the one who lent Cotton Mather the *Philosophical Transactions* journal, found many things in these inoculation practices to take exception with (fig. 2). He proclaimed Boylston a "quack" and deemed inoculation a criminal act that was ineffective at producing immunity to smallpox. Claims and rebuttals were thrown back and forth, only to further divide a community into strife.[11]

Despite this divide, inoculation was still performed, but nowhere near the rate needed for effective prevention. By the end of September 1721, 2,757 people in Boston were naturally infected with smallpox, and by the end of October, 411 died of smallpox. This festering of smallpox mirrored the continued feud between parties. The disagreement became violent on November 11th, when a homemade bomb with a note addressed to Mather was thrown through his bedroom window overnight. The bomb did not detonate, but the message was delivered.[11]

By February 1722, Boston officials announced that no smallpox cases remained in the city. By this point, the virus had exhausted its habitable hosts leaving just the naturally immune and resistant left. The data from the event showed in favor of inoculation, with a mortality rate of 15% in naturally infected people versus <2.5% in inoculated people. The squabbling about inoculation practices did not cease, but did calm as time went on. Contributions from Mather and Boylston helped with the development of preventative medical practices, such as in 1777 when General George Washington mandated inoculation for smallpox for all continental soldiers.[11,12]

The unfolding of this controversy has much in common with countless modern-day examples, such as the MMR

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levels of these patients (normal TSH level in 82.7% vs 84.5%, *P* = 0.07).[13] Another study from 2020 by Brito JP et al. compared generic levothyroxine to brand name levothyroxine preparations. The retrospective study found no clinically significant differences among patients using either the generic or brand (normal TSH levels in 82.6% vs 83.8%, *P* = 0.62).[14] These studies suggest that the different preparations of levothyroxine have greater bioequivalence than previously suspected. Based on recent findings, this data fulfills what the ATA was hoping for and could possibly result in a change in guideline recommendations in the future.

Levothyroxine began as the use of extracted healthy thyroid gland and has developed into one of the most common medications prescribed in the United States. The discovery of T3, the use of radioactive iodine, and the discovery of the relationship between T4 and T3 all led to increased confidence in the effectiveness of levothyroxine. Since its introduction to the United States, the drug has faced scrutiny about stability and equivalence among generics. Levothyroxine has been viewed as an important medication since its first use in 1891 and will continue to be one of the most widely used medications in the future.[3]

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vaccine in 1998, the HPV vaccine in 2006, and most recently, the 2020 COVID-19 vaccine.[12-14] The specific fears may not be the same, but reasons for distrust are strikingly similar: apprehension from a religious standpoint, lack of faith in the safety of the practice, questioning the training and credentials of those responsible, and dissemination of inaccurate information. This is not to say that all medical practices should be innately accepted, for modern medicine is most beneficial when safety and efficacy is investigated, documented, and reviewed.

This historical summary highlights the complex interplay between innovation and resistance when it comes to public health promotion. The challenges Mather and Boylston faced mirror those seen in contemporary debates over vaccination, reminding us of the importance of careful scientific inquiry, effective communication, and open-mindedness in overcoming public health crises. The lessons from the past remain relevant in ensuring that medical advances continue to be embraced for the greater good.

Fig. 1: Description: Two men—one vaccinated against smallpox, the other not vaccinated—and the resulting difference.

Source: "A contemporary photograph of vaccinated and non-vaccinated men with smallpox from 1904, demonstrating the effects of immunization," *The College of Physicians of Philadelphia Digital Library."* Accessed November 28, 2024, https://cppdigitallibrary.org/items/show/8157.

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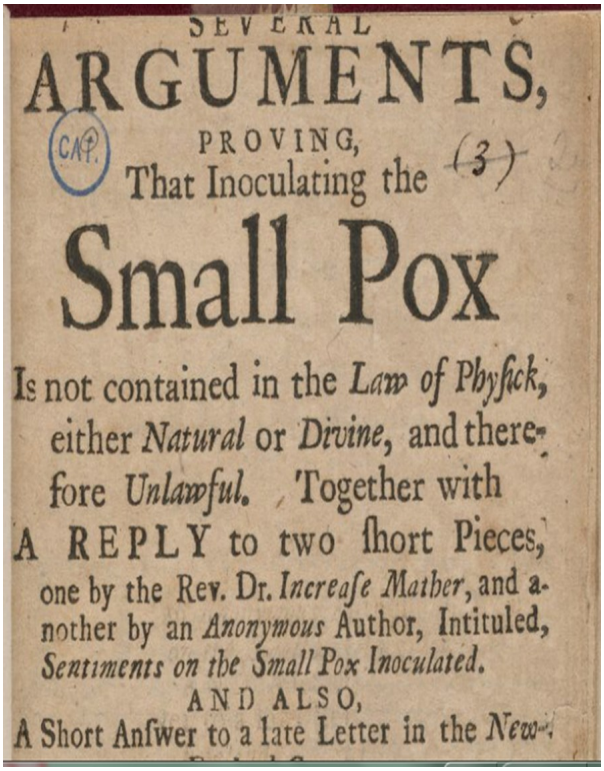
SEVERAL
ARGUMENTS,
PROVING,
That Inoculating the
Small Pox
Is not contained in the *Law of Phyſick*, either *Natural* or *Divine*, and therefore *Unlawful*. Together with
A REPLY to two ſhort Pieces, one by the Rev. Dr. *Increaſe Mather*, and another by an *Anonymous* Author, Intituled, *Sentiments on the Small Pox Inoculated*.
AND ALSO,
A Short Anſwer to a late Letter in the *New-*

Fig. 2: Description: A letter addressed to Alexander Stuart, dated Feb. 15, 1722. Attributed to William Douglass in the Library of Congress catalog.

Source: *The abuses and scandals of some late pamphlets in favour of inoculation of the small pox, modestly obviated, and inoculation further consider'd in a letter to a-s-M.d. & F.R.S. in London; Abuses and scandals of some late pamphlets in favour of inoculation; Vindication of the ministers of Boston; Postscript to abuses, &c. obviated. (n.d.).* Contagion—CURIOSity Digital Collections.. https://curiosity.lib.harvard.edu/contagion/catalog/36-99023074880203941.

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cortex within those with AD versus healthy individuals.[8] This led to the idea that anticholinesterases, such as galantamine, may be helpful in the early stages of the disease.[3,8]

Galantamine exerts its pharmacological effects in two ways. Firstly, galantamine binds to the active site of acetylcholinesterase allowing for acetylcholine to accumulate in the synaptic cleft and improve the transmission of cholinergic nerves.[6] This in turn improves cognition in patients.[6] The second function is that galantamine selectively and allosterically binds to the presynaptic and postsynaptic nicotinic acetylcholine receptors on cholinergic neurons.[6] When galantamine is bound to these receptors, their response to acetylcholine is intensified and promotes the release of neurotransmitters that are important for memory.[6] This selective dual mechanism has been found to increase patient tolerability compared to other AD therapies.[6] With the neurodegenerative nature of AD, galantamine does not exert any effect on the biological processes involved.[2]

Galantamine's uses over the years

Galantamine was originally studied in myopathies and post-polio paralytic conditions as well as a reversal agent for neuromuscular blockade.[2] The first application of galantamine in this setting was in 1960 by scientists Derejan and Krasteva.[5] Several other articles between 1962 and 1971 considered the use of galantamine as an effective antidote for non-depolarizing neuromuscular blocking agents, such as tubocurarine, gallamine, diplacinum, alcuronium, and pancuronium.[5] H. Foitzik (1973), describes the use of galantamine versus neostigmine in patients who underwent laparotomies with anesthesia and pancuronium as a neuromuscular blocking agent.[9] Studies were conducted between 1956 and 1963 to observe galantamine's effect on poliomyelitis.[5] The most notable observations were from Revelli and Grasso in 1962.[5] In 52 acute-stage poliomyelitis patients treated with galantamine, 27 patients experienced complete rehabilitation.[5]

Many scientists from various countries also conducted research to observe the effects of galantamine on myasthenia gravis over the years. Some of the studies conducted in the early 1960s by Irwin, Smith, Mashkovsky, and Altshuler found that galantamine inhibited muscular cholinesterase more than pyridostigmine but less than neostigmine, both of which are commonly used for the treatment of myasthenia gravis.[5]

Galantamine's inhibition of acetylcholinesterase inspired researchers to study its use in various psychiatric disorders such as mild cognitive impairment, cognitive impairment in schizophrenia and bipolar disorder, and autism.[2] J.E. Sweeney at John Hopkins University in 1988 evaluated the effect of galantamine on the spatial memory of mice.[10] The mice with lesions on their basal forebrains showed major improvements in their working memory when given galantamine compared to placebo.[10] On February 28th, 2001, the FDA approved galantamine 4 mg and 8 mg tablets for the treatment of mild to moderate dementia due to AD.[11,12]

Previously used medications for Alzheimer's Disease

Physostigmine is an alkaloid found in both the Calabar bean plant (*Physostigma venenosum*) and the manchineel tree (*Hippomane mancinella*) in West Africa.[13,14] Prior to the 1400s, this naturally toxic compound was used by native tribes in West Africa for a trial by or-

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deal.[13,14] The trial forced individuals suspected of witchcraft to ingest a potion containing physostigmine to prove their innocence.[14] If the accused person vomited within a half-hour, they were innocent, but if the patient succumbed to the poison, they were found guilty.[14] It wasn't until the 15th century that physostigmine was discovered by European scientists and introduced into early medical practice.[14] In 1855, Sir Robert Christison was the first to discover the lethal effect of physostigmine through performing experiments on himself.[14] He ingested a small portion of the calabar bean on an empty stomach, inducing its toxic effects, but was able to reverse it by inducing vomiting with soapy water.[14] In 1863, a British physician and pharmacologist Thomas Fraser was the first to isolate the compound and describe its effect on the body.[14] His studies mainly focused on physostigmine's ocular properties such as constriction of the pupils, relaxation of the ciliary muscles, and enhancement in aqueous humor outflow which decreases intraocular pressure.[14] Fraser's discovery led to the use of physostigmine to treat glaucoma.[14] Additionally, scientists attempted to use physostigmine in many other medical situations including fecal and urinary incontinence, myasthenia gravis, and ataxia.[14] In 1935, Dr. Percy L. Julian was the first to synthesize physostigmine in a laboratory setting.[15] Julian's achievement allowed for physostigmine to be readily available for glaucoma treatment, and for further research studies.[15] Several studies conducted in the 1970s showed that the use of physostigmine could improve the memory of patients with and without dementia.[16] Ultimately, the use of physostigmine was determined to be an unsuitable treatment for AD based on subsequent studies showing inconsistent benefits, short half-life, and harsh side effects.[13,16] Today, physostigmine is currently being used as a reversal agent for toxic anticholinergic effects.

Tacrine was first synthesized in 1940 by Adrian Albert at the University of Sydney with the intent to make a potent antiseptic to treat wounded troops.[17,18] Although Tacrine ended up lacking any antiseptic properties, Frank Shaw and Geoffrey Bentley did discover that in animal studies, tacrine was able to antagonize the effects of respiratory depression and sedation associated with morphine.[17,18] This finding enabled terminal cancer patients to receive higher doses of morphine without increased risk of respiratory depression.[17,18] In 1961, Heilbron first described the mechanism of action for tacrine as an acetylcholinesterase and butyrylcholinesterase inhibitor.[19] Utilizing in vitro studies, she was able to demonstrate that tacrine acted as a reversible, partially competitive inhibitor of acetylcholine and a more potent inhibitor of butyrylcholine.[19] In 1980, William Summers, et al discovered that tacrine could be used to reverse anticholinergic syndromes caused by tricyclic antidepressant overdoses.[20] In 1981, Summers and Sam Gershon conducted a clinical study in 12 patients with AD in which these subjects were given IV tacrine.[20] The study found that 9 out of the 12 patients had short-term memory benefits.[20] In September of 1993, Cognex (tacrine) became the first agent FDA approved for the treatment of cognitive symptoms related to AD.[20] Tacrine was discontinued in 2013 due to its many side effects including nausea, vomiting, decrease in appetite, and hepatotoxicity.[21]

Donepezil, a tacrine-derivative, is a reversible, non-competitive inhibitor of acetylcholinesterase.[21] Donepezil was developed in 1983 by Eisai pharmaceutical company.[21] The researchers at Eisai began conducting clinical trials to investigate its efficacy in AD patients.[22] In 1996, donepezil was approved for treating mild to moderate AD after a phase III trial conducted in Japan showed that the use of donepezil led to significantly higher improvement rates in AD-clinical rating scales compared to a placebo.[22] In 2010, donepezil was approved for use in moderate to severe AD with a maximum dose of 23 mg/day.[21] The donepezil transdermal patch was FDA-approved in 2022.[23]

Rivastigmine is a semisynthetic derivative of physostigmine and acts as a non-competitive, pseudo-irreversible inhibitor of acetylcholinesterase.[21,22] In the 1980s, the drug was developed by Dr. Marta Weinstock-Rosin at Hebrew University in Israel.[13] Rivastigmine was acquired by Novartis in 1985 and was eventually marketed under the name Exelon.[13] In 2000, rivastigmine was approved for use in mild to moderate AD at a starting daily dose of 3 mg and a maximum dose of 6 mg twice daily.[21,22] Similar to Donepezil, a rivastigmine 24-hour patch was approved in 2007 for the treatment of mild to moderate AD.[21]

Memantine, a derivative of amantadine, is a competitive N-methyl-D-aspartate (NMDA) antagonist that works by blocking the effects of glutamate leading to decreased excitability and excessive stimulation that occurs in AD.[23] Eli Lilly originally patented the drug in 1966 as an antidiabetic agent; however, clinical studies showed that memantine was not successful in managing blood sugar levels.[23] In 1982, a German pharmaceutical company conducted extensive research on memantine and discovered that the drug exhibited central nervous system activity.[23] In 1986, researchers began conducted clinical studies to assess the benefit of memantine in patients with dementia and in 1989, memantine was approved for use in Germany.[23,24] In 2000, Merz and Lundbeck pharmaceutical company submitted a new drug application (NDA) to the FDA for the treatment of moderate to severe AD.[23] The drug was FDA-approved in 2003 for moderate to severe AD under the trade name Namenda.[23]

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Recent innovations with galantamine

In January 2005, it had been suggested that at least 10 patients who had been prescribed Reminyl (galantamine's first trade name) had been instead dispensed a drug indicated for the treatment of type 2 diabetes mellitus, Amaryl (glimepiride).[25] This resulted in the death of 2 patients, which has been attributed to the wrongful dispensing of similarly named medications likely due to both having had 4 mg doses.[25] Ortho-McNeil Neurologics Inc. had begun a rebranding campaign in October 2004 following FDA officials' concerns surrounding these 2 therapies and their potential for look-alike-related issues.[26] Thus, Reminyl was rebranded as Razadyne and in 2005 the immediate-release Razadyne was introduced alongside the new, extended-release form approved in December 2004, Razadyne ER which are both available today.[26]

With the need for new AD medications, galantamine was revisited and a prodrug (GLN-1062) was developed by the German pharmaceutical company, Galantos Pharma. Marketed under the brand name, Memogain, the nasally inhaled GLN-1062 showed an increased ability for transport into the central nervous system (CNS) due to its lipophilic nature resulting in an up to 15-fold CNS concentration compared to galantamine.[27] GLN-1062 was sold in 2020 to Canadian developer Neurodyn which was later renamed to Alpha Cognition Inc. and GLN-1062 was rebranded to ALPHA-1062 for promotion by the current developer.[28] On July 29, 2024 the FDA approved ALPHA-1062 for the treatment of AD and marketing commenced for benzgalantamine (formerly ALPHA-1062), the brand name of Zunveyl.[29] Benzgalantamine is a prodrug of galantamine for oral administration with both instant and extended-release dosage forms.[30] Additionally, Alpha Cognition has called ALPHA-1062 a "new generation" acetylcholinesterase inhibitor with plans to implement a nasally inhaled product combining ALPHA-1062 with memantine.[31]

Conclusion:

Galantamine's history serves as an example of useful plant compounds being discovered through traditional use and observation. Though other significant treatments exist for AD, galantamine has shown great success since the 1990s with recent advancements in formulations providing more efficacy and value to its overall use in history. AD has vicious implications as an ailment for which there is no cure and for which there is a great need for progression-slowing treatments. Likely, the world has not seen an end to future innovative uses of galantamine.

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