Parkinsonism

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Abstract

NOTE - this document is in draft currently. If I have the discipline, I will be making additions and edits for the next few months

Parkinsonism is a category of neurological diseases characterized primarily by motor symptoms such as bradykinesia, rigidity, and resting tremor. Specific diseases include Parkinson's Disease (PD), Lewy Body Dementia (LBD), Multiple System Atrophy (MSA), and Progressive Supranuclear Palsy (PSP). While these disorders share overlapping clinical features, their underlying pathologies are complex and heterogeneous. Common pathological features among many forms of idiopathic parkinsonism include misfolded proteins leading to toxic intracellular aggregates, dysfunctional mitochondria resulting in impaired energy production and oxidative stress, chronic central nervous system (CNS) inflammation, and impaired cellular machinery that normally maintains protein homeostasis. The diseases diverge based on the specific cell types affected, the protein that aggregates (e.g., alpha-synuclein in PD, LBD, and MSA; tau in PSP), and the regions of the brain impacted. These pathological changes are reflected in the cargo of exosomes—small extracellular vesicles released by affected cells—which may contain misfolded proteins, markers of mitochondrial dysfunction, inflammatory mediators, and molecular indicators of impaired cellular maintenance. Because exosomes can cross the blood-brain barrier and enter peripheral fluids, they represent a promising avenue for non-invasive biomarker discovery, potentially enabling earlier diagnosis and improved monitoring of disease progression in parkinsonian disorders.

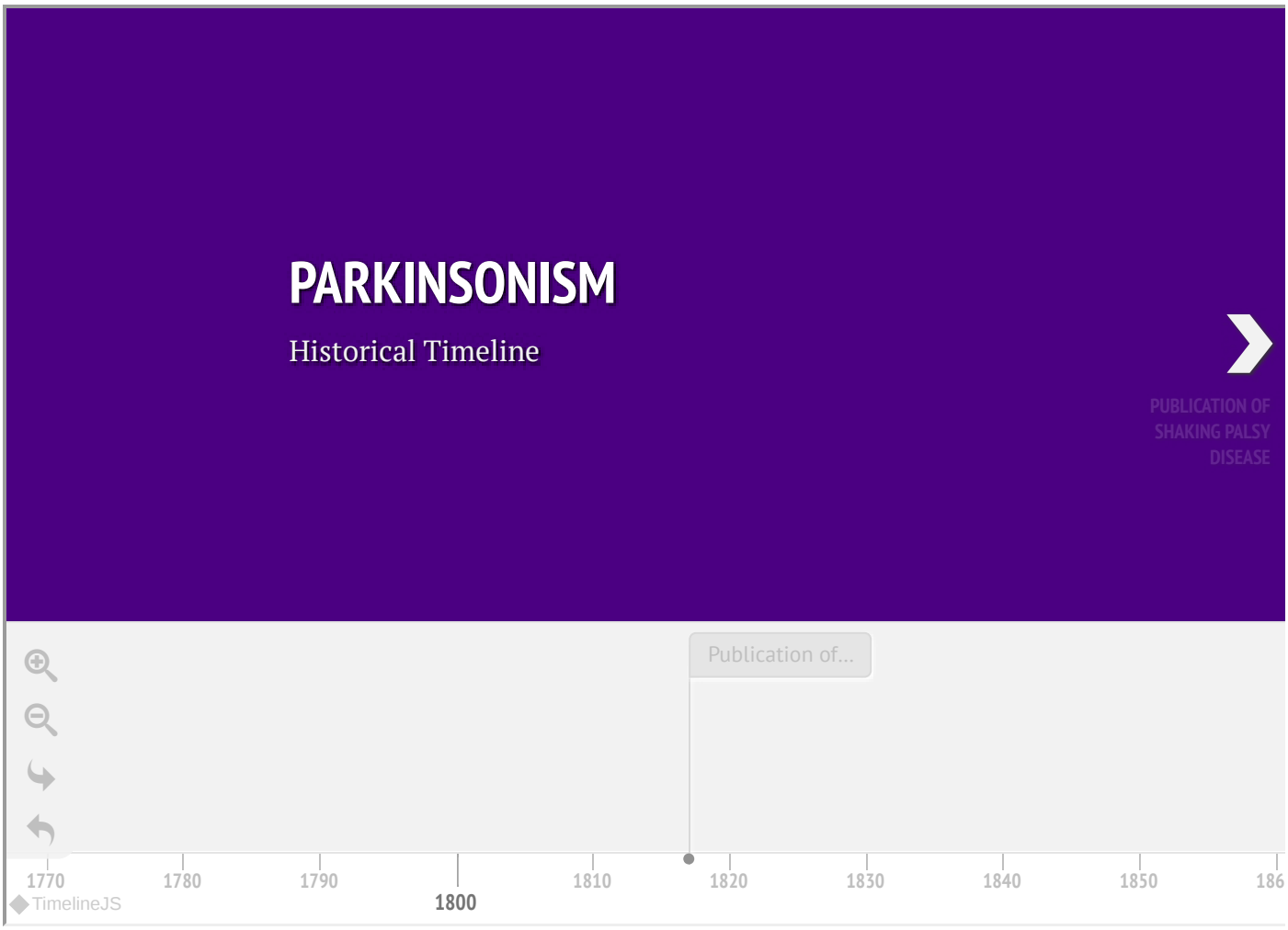
Introduction

The history of Parkinsonism began in 1817, when James Parkinson published An Essay on the Shaking Palsy, describing the characteristic motor symptoms of the condition that would later bear his name. Several decades later, Jean-Martin Charcot refined Parkinson's observations, distinguishing the disease from other movement disorders and formally naming it Maladie de Parkinson. Charcot also noted degeneration of the substantia nigra, an insight later validated as a central pathological feature. Around 1900, Dejerine and Thomas described a distinct degenerative disorder now recognized as Multiple System Atrophy (MSA). Although its pathology differs from Parkinson's Disease, MSA shares overlapping motor symptoms and is often confused with PD in clinical settings—a confusion made more understandable by the later discovery that both diseases involve toxic aggregates of misfolded alpha-synuclein. In 1912, Friedrich Lewy identified intraneuronal inclusions—later called Lewy bodies—marking the first visible pathological hallmark of PD, though their significance would remain unclear for decades.

The mid-20th century brought a major breakthrough when Arvid Carlsson demonstrated the essential role of the neurotransmitter dopamine in motor control and its abundance in the basal ganglia, laying the groundwork for understanding its depletion in Parkinson's Disease (PD). This discovery led to dopamine-replacement therapy, culminating in the widespread use—and eventual FDA approval in 1975—of carbidopa/levodopa, which remains the cornerstone of PD treatment and is also the mainstay therapy for Multiple System Atrophy (MSA), despite its typically limited and short-lived benefits. In the 1980s, an unexpected insight came when individuals exposed to heroin laced with the synthetic drug MPTP developed rapid-onset parkinsonism. The compound's inhibition of mitochondrial Complex I exposed the particular vulnerability of dopaminergic neurons to environmental toxins, marking a pivotal shift away from symptomatic treatments toward mechanistic studies focused on the cellular underpinnings of PD. Subsequent investigations uncovered key roles for mitochondrial dysfunction, oxidative stress, and impaired protein clearance. In the 1990s, mutations in the SNCA gene, which encodes the alpha-synuclein protein, confirmed it as a causative factor in familial PD, and

misfolded alpha-synuclein aggregates were identified as the major component of Lewy bodies, cementing the protein's central role in both inherited and sporadic forms of the disease.

Building on this mechanistic shift, Heiko Braak proposed in 2002 and 2003 that Parkinson's Disease (PD) may originate outside the brain, with misfolded alpha-synuclein initially appearing in the enteric nervous system or olfactory bulb and then spreading in a prion-like fashion to the central nervous system (CNS). Although originally developed to describe PD, similar peripheral origins have been explored for Multiple System Atrophy (MSA), particularly given its early autonomic symptoms—such as constipation, urinary dysfunction, and orthostatic hypotension—and the detection of alpha-synuclein pathology in the peripheral nervous system. More recently, Filip Scheperjans and others have expanded this line of inquiry by implicating the gut microbiota in triggering the chronic inflammation and immune dysregulation that may drive early alpha-synuclein misfolding. These findings have reframed Parkinson's research, and increasingly MSA research as well, shifting focus from late-stage neurodegeneration to the search for prodromal biomarkers and early therapeutic intervention.



All of these scientific developments—from Lewy's discovery to Braak's hypothesis and the rise of microbiome research—have expanded our understanding of Parkinsonism. Yet despite this progress, the clinical diagnosis of Parkinson's Disease (PD) and Multiple System Atrophy (MSA) remains largely reliant on neurologists' evaluation of motor symptoms—such as tremor, rigidity, balance, and coordination—which only manifest well after disease onset. Moreover, these symptoms overlap considerably between PD and MSA, making accurate differentiation difficult in early stages. While several promising biomarkers are under investigation, none are currently used as a front-line diagnostic tool. The closest example, a synuclein-positive skin biopsy, is typically reserved for

confirmatory use after clinical suspicion has already been established. This gap underscores the need for sensitive, disease-specific biomarkers capable of identifying Parkinsonism early—ideally in its prodromal phase—when therapeutic intervention may be most effective.

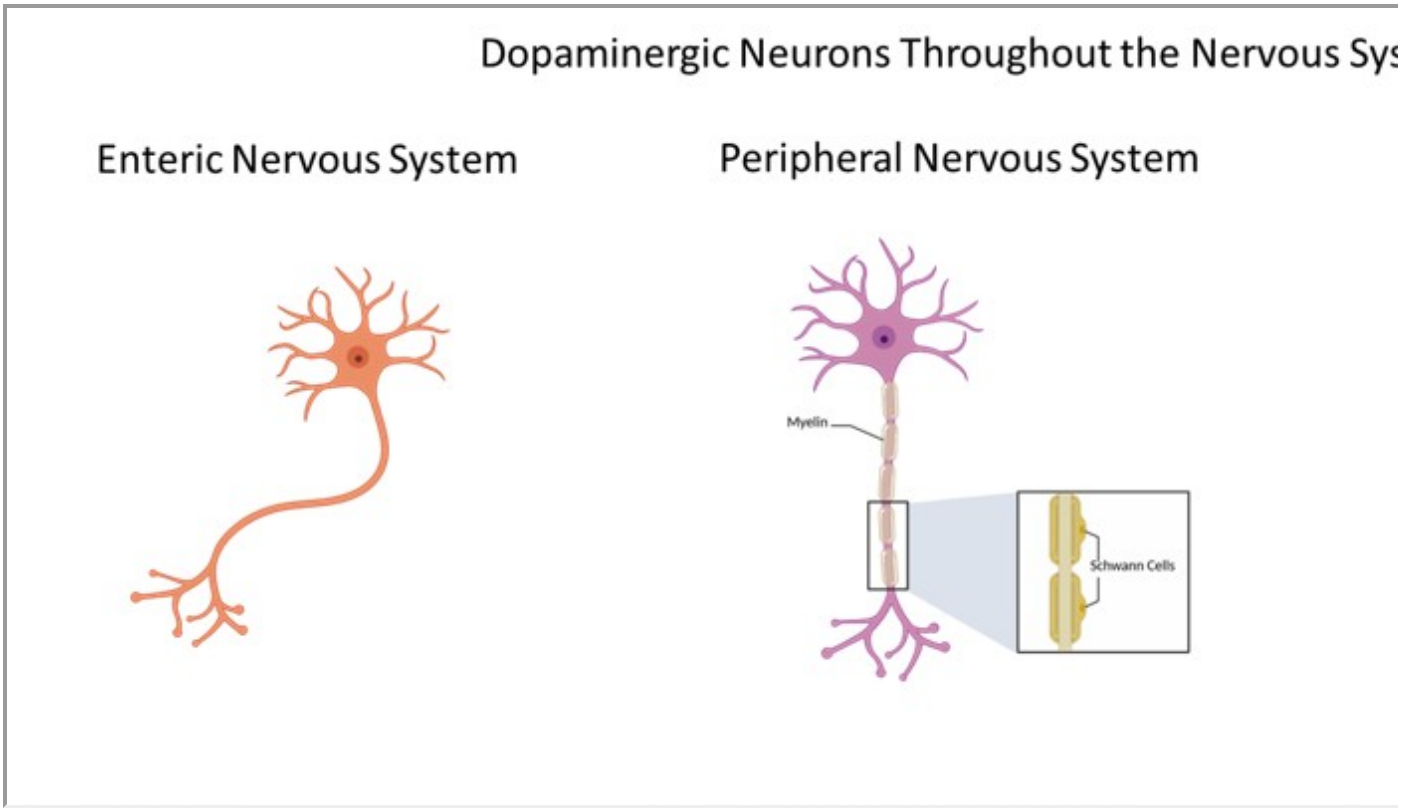
Peripheral Gateways to Pathogenesis

Peripheral structures like the intestinal lining and olfactory epithelium—first proposed as sites of disease initiation in Braak's staging framework—have emerged as potential gateways for the development of Parkinson's Disease (PD) and Multiple System Atrophy (MSA), offering early access points through which environmental triggers may influence disease onset and progression. Of these, the intestinal lining has received the most sustained attention, particularly as a site where breaches in the epithelial barrier may allow microbial products or toxins to interact directly with neurons, glia, and immune cells. Misfolded α-synuclein originating in this environment may then propagate to the central nervous system via the vagus nerve. While Braak's hypothesis initially emphasized anatomical spread, subsequent research has expanded its scope, implicating the gut microbiota and intestinal immune signaling in both initiating and sustaining the chronic inflammation that drives early protein misfolding. These findings have reframed the intestinal mucosa as a dynamic interface—one where microbial, immune, and neuronal signals converge to shape vulnerability or resilience.

Intestinal Lining

Mounting evidence suggests that the pathogenesis of neurodegenerative diseases like Parkinson's Disease (PD) may begin in the Enteric Nervous System (ENS), progress through the autonomic branches of the Peripheral Nervous System (PNS), and ascend via a neural bridge—most notably, the vagus nerve—into the Central Nervous System (CNS). While this ENS-to-CNS progression is well supported in PD, similar pathways are being explored in Multiple System Atrophy (MSA), especially in cases where early autonomic symptoms and peripheral alpha-synuclein pathology are evident. Understanding the structural anatomy of these three interconnected systems is therefore critical to realizing how synucleinopathies may develop and spread through the body. A key to this understanding lies in comparing dopaminergic neurons as they appear in each of these environments: the Enteric Nervous System (ENS), the Peripheral Nervous System (PNS), and the Central Nervous System (CNS). These comparisons not only illustrate structural distinctions but also highlight how each system is uniquely affected in diseases like PD and MSA.

To visually anchor this comparison, we present a labeled illustration of representative neurons from each system. This drawing forms the centerpiece of this section and includes bullet points beneath each neuron to highlight their key structural and functional characteristics. These visual summaries also reinforce each system's relevance to synucleinopathies like PD and MSA.



Enteric Nervous System (ENS) Neuron

Although the ENS is technically a subdivision of the autonomic branch of the Peripheral Nervous System (PNS), its extensive autonomy and structural specialization justify its separate discussion here. The ENS resides in the walls of the gastrointestinal tract, primarily within the myenteric and submucosal plexuses. These plexuses are dense, highly branched networks of unmyelinated neurons and enteric glial cells. Rather than transmitting long-range signals, these neurons coordinate complex, localized reflexes to control gut motility, secretion, and blood flow. The unmyelinated nature of ENS neurons facilitates tight packing and high-density connectivity, which is critical for fine-tuned digestive control.

Importantly, research suggests that alpha-synuclein pathology may begin in this region, with misfolded protein appearing in the enteric plexus before spreading via autonomic pathways to the CNS. This supports Braak's hypothesis that synucleinopathies such as PD and possibly MSA may originate in the gut.

Peripheral Nervous System (PNS) Neuron

PNS neurons bridge the gap between the CNS and the digestive tract and other visceral organs. They are frequently myelinated by Schwann cells, each of which wraps a single axonal segment. This design supports rapid conduction of autonomic signals critical for regulating functions like blood pressure and digestion. In the context of PD and MSA, the PNS is a useful diagnostic window: alpha-synuclein pathology can be detected in skin and autonomic nerves even in the prodromal phase of disease.

A notable distinction between PD and MSA lies in the extent of autonomic dysfunction seen in the PNS. MSA often presents with earlier and more severe autonomic symptoms—such as orthostatic hypotension, urinary incontinence, and erectile dysfunction—compared to PD. This greater impact on autonomic systems contributes directly to the term "multiple system atrophy," reflecting degeneration that extends beyond the motor system.

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Central Nervous System (CNS) Neuron

CNS neurons reside within the brain and spinal cord and play integrative roles in everything from motor control to higher cognitive function. They are myelinated by oligodendrocytes, which can extend processes to multiple axons. Uniquely, a single oligodendrocyte can myelinate axons from multiple types of neurons—such as dopaminergic, GABAergic, and serotonergic—contributing to the efficiency and interconnectivity of CNS signaling. This allows for high-efficiency signal propagation across vast brain regions. In PD, CNS dopaminergic neurons degenerate, particularly in the substantia nigra. In MSA, it is the oligodendrocytes themselves that become pathological, forming glial cytoplasmic inclusions of misfolded alpha-synuclein.

One distinguishing feature of MSA is that demyelination occurs across a broad range of neuron types. The death of oligodendrocytes leads to widespread disruption of myelin sheaths, affecting not only dopaminergic neurons but also serotonergic, cholinergic, and other neuron classes. This loss of structural insulation impairs axonal function and triggers apoptotic cell death, contributing to the multisystem nature of degeneration observed in MSA.

By anchoring this anatomical comparison with a clear illustration and accompanying bullet points, we can directly visualize how structural differences in neuron types contribute to both healthy function and disease vulnerability.

A Broad Selection of Potential Early Detection Biomarkers

Biomarker	Category	Applicable Disorders	Source Fluid/Tissue
α-Synuclein Oligomers	Disease-specific	PD, MSA, DLB	CSF, Blood
Total α-Synuclein	Disease-associated	PD, MSA, DLB	CSF
Phosphorylated α-Synuclein	Disease-specific	PD	CSF
Neurofilament Light Chain (NfL)	Disease-associated	PD, MSA, PSP, CBD	CSF, Blood
Total Tau Protein	Disease-associated	PD, MSA, DLB, AD	CSF
Phosphorylated Tau Protein	Disease-associated	AD, DLB	CSF
Amyloid-β42	Disease-associated	AD, DLB	CSF
DJ-1 Protein	Disease-associated	PD	CSF, Blood
Lysosomal Enzymes	Disease-associated	PD, MSA	CSF
Inflammatory Cytokines (e.g., IL-6, TNF-α)	Disease-associated	PD, MSA, PSP, CBD	CSF, Blood

Biomarker	Category	Applicable Disorders	Source Fluid/Tissue
MicroRNAs (e.g., miR-34b/c, miR-133b)	Disease-associated	PD	Blood, CSF
PINK1/Parkin Levels	Disease-associated	PD, MSA	Blood, CSF
Complement Proteins (e.g., C3, Factor H)	Disease-associated	PD, MSA	CSF

Note: PD = Parkinson's Disease; MSA = Multiple System Atrophy; DLB = Dementia with Lewy Bodies; PSP = Progressive Supranuclear Palsy; CBD = Corticobasal Degeneration; AD = Alzheimer's Disease

Exosomes

Exosomes are small extracellular vesicles that play a key role in cell-to-cell communication and waste removal by transporting molecular cargo such as proteins, RNA, and lipids. Research within the last decade has focused on their potential in targeted therapy delivery, disease biomarker discovery, immune system modulation, and strategies to block their uptake to mitigate pathological processes. [Citation Needed]

Regarding neurodegenerative diseases, exosomes are being studied as potential biomarkers for early diagnosis, particularly for disorders like Parkinson's Disease and Multiple System Atrophy. [Citation Needed] These diseases have long prodromal phases, during which symptoms may be subtle or non-motor in nature, delaying diagnosis until neurodegeneration is already advanced. Since current diagnostic methods rely heavily on clinical evaluations of motor dysfunction, the identification of exosome-based biomarkers could enable earlier, more precise detection. Importantly, clinically viable biomarkers must be detectable in peripheral fluids such as blood or saliva, allowing for non-invasive testing during routine healthcare visits. This could shift the diagnostic paradigm from symptom-based assessments to proactive screening, potentially enabling earlier interventions that slow disease progression.

Importantly, exosomes can cross the blood-brain barrier (BBB) bidirectionally, [Citation Needed] allowing for the collection of CNS biomarkers in peripheral fluids and enabling potential therapeutic delivery to the brain. However, in neurodegenerative diseases, a compromised BBB may also permit the entry of exosomes carrying toxic cargo, potentially contributing to disease progression by spreading misfolded proteins, exacerbating neuroinflammation, and inducing metabolic stress. Additionally, exosomes can transport immune-modulating factors, such as cytokines or microRNA, which may further disrupt CNS homeostasis. Understanding these mechanisms is critical, as exosomes could serve as both pathological agents and therapeutic targets in neurodegenerative disease management. [Citation Needed]

Beyond their role in disease progression, exosomes also serve as natural concentrators of key biomarkers, which might otherwise be too dilute in peripheral fluids like blood or saliva for reliable detection. Furthermore, exosomes carry surface antigens reflective of their parent cells, allowing for selective isolation of disease-relevant exosomes. [Citation Needed] By isolating exosomes derived from specific cell types, such as dopaminergic neurons or oligodendrocytes, researchers can obtain enriched biomarker profiles in measurable concentrations, enhancing disease detection. This makes exosome-based diagnostics a promising avenue for the early identification and monitoring of neurodegenerative conditions.

Exosomes Cargo and Key Biomarkers

Some text....

Future Directions and Translational Implications

Despite significant advances in our mechanistic understanding of Parkinson's Disease (PD) and Multiple System Atrophy (MSA), clinical diagnosis remains fundamentally reactive—triggered by overt motor symptoms that arise well after disease onset. Even when PD and MSA are correctly identified, treatment remains largely symptomatic, with little to no impact on long-term progression. Yet early and accurate differentiation still carries meaningful value. For patients and families, it shapes prognosis, expectations, and long-term planning. For clinicians, it informs therapeutic priorities, including the decision to avoid prolonged levodopa trials in likely MSA cases. And for researchers, it allows cleaner stratification in clinical trials and accelerates the development of disease-specific interventions.

Looking ahead, early diagnostic clarity may also enable cross-disease therapeutic repurposing. Although MSA is rare and underrepresented in drug development pipelines, it shares key downstream pathologies with more common disorders. One such overlap is with Multiple Sclerosis (MS), where demyelination—though driven by autoimmune mechanisms—results in similar oligodendrocyte dysfunction and axonal compromise. If emerging MS therapies aimed at remyelination or glial support prove safe and broadly effective, they may offer therapeutic potential for MSA as well, particularly when initiated during its early, preclinical phase.

This principle echoes the trajectory of CAR-T cell therapy, which was first developed and approved for common hematologic malignancies like leukemia and lymphoma before being adapted to treat multiple myeloma. Although the diseases differ in etiology, they share enough downstream immunological architecture to allow therapeutic crossover. The same logic may apply in neurology: therapies developed for more prevalent demyelinating diseases like MS may hold untapped potential in rare disorders such as MSA—and early diagnosis of MSA may enable timely exploration.

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The rest of this document is a full list of formatting elements/features supported by Manubot. Compare the input (`.md` files in the `/content` directory) to the output you see below.

Basic formatting

Bold text

Semi-bold text

Italic text

Combined *italics and* ***bold***

~~Strikethrough~~

1. Ordered list item
2. Ordered list item
    a. Sub-item
    b. Sub-item
        i. Sub-sub-item
3. Ordered list item
    a. Sub-item

- List item
- List item
- List item

subscript: H_2O is a liquid

superscript: 2^{10} is 1024.

unicode superscripts^{0123456789}

unicode subscripts$_{0123456789}$

A long paragraph of text. Lorem ipsum dolor sit amet, consectetur adipiscing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip ex ea commodo consequat. Duis aute irure dolor in reprehenderit in voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit anim id est laborum.

Putting each sentence on its own line has numerous benefits with regard to editing and version control.

Line break without starting a new paragraph by putting
two spaces at end of line.

Document organization

Document section headings:

Heading 1

Heading 2

Heading 3

Heading 4

Heading 5

Heading 6

A heading centered on its own printed page

Horizontal rule:

`Heading 1`'s are recommended to be reserved for the title of the manuscript.

`Heading 2`'s are recommended for broad sections such as *Abstract*, *Methods*, *Conclusion*, etc.

`Heading 3`'s and `Heading 4`'s are recommended for sub-sections.

Links

Bare URL link: https://manubot.org

Long link with lots of words and stuff and junk and bleep and blah and stuff and other stuff and more stuff yeah

Link with text

Link with hover text

Link by reference

Citations

Citation by DOI [1].

Citation by PubMed Central ID [2].

Citation by PubMed ID [3].

Citation by Wikidata ID [4].

Citation by ISBN [5].

Citation by URL [6].

Citation by alias [7].

Multiple citations can be put inside the same set of brackets [1,5,7]. Manubot plugins provide easier, more convenient visualization of and navigation between citations [2,3,7,8].

Citation tags (i.e. aliases) can be defined in their own paragraphs using Markdown's reference link syntax:

Referencing figures, tables, equations

Figure 1

Figure 2

Figure 3

Figure 4

Table 1

Equation 1

Equation 2

Quotes and code

> Quoted text

> Quoted block of text
>
> Two roads diverged in a wood, and I—
> I took the one less traveled by,
> And that has made all the difference.

Code `in the middle` of normal text, aka `inline code`.

Code block with Python syntax highlighting:

```
from manubot.cite.doi import expand_short_doi

def test_expand_short_doi():
    doi = expand_short_doi("10/c3bp")
    # a string too long to fit within page:
    assert doi == "10.25313/2524-2695-2018-3-vliyanie-enhansera-copia-i-
        insulyatora-gypsy-na-sintez-ernk-modifikatsii-hromatina-i-
        svyazyvanie-insulyatornyh-belkov-vtransfetsirovannyh-geneticheskih-
        konstruktsiyah"
```

Code block with no syntax highlighting:

```
Exporting HTML manuscript
Exporting DOCX manuscript
Exporting PDF manuscript
```

Figures

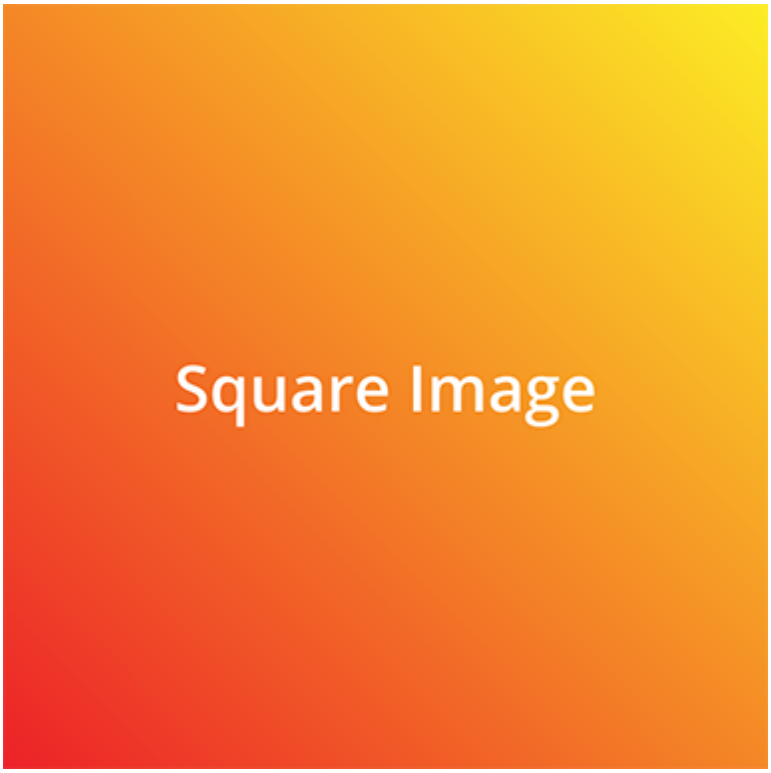

Figure 1: A square image at actual size and with a bottom caption. Loaded from the latest version of image on GitHub.

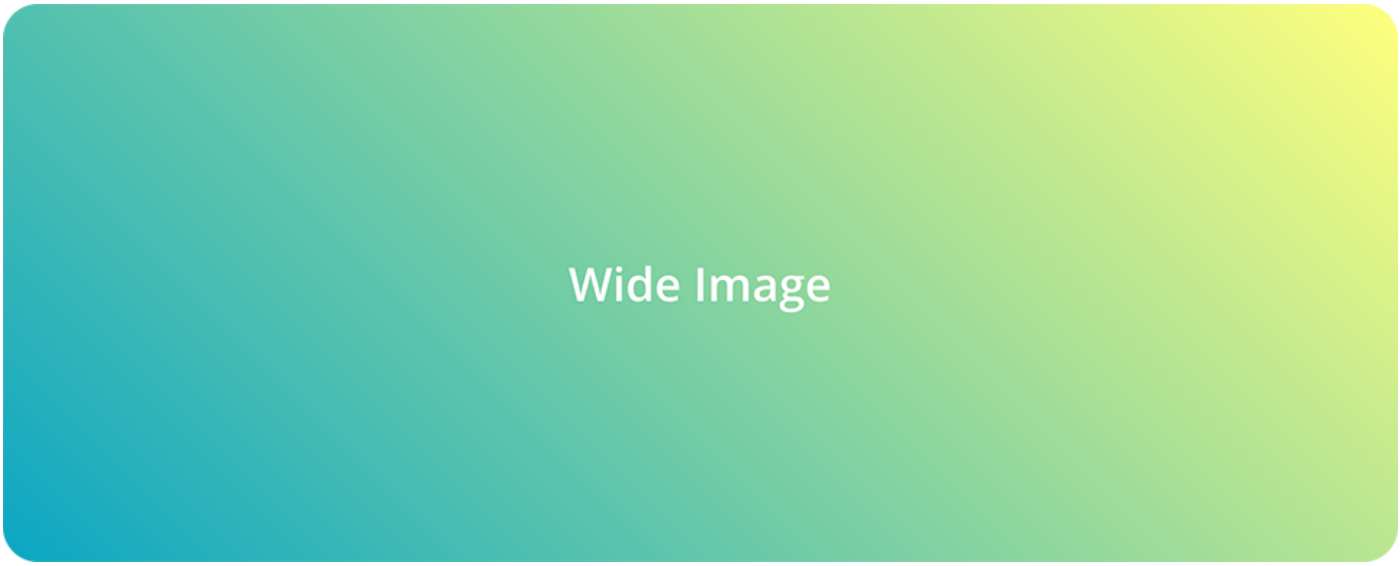

Figure 2: An image too wide to fit within page at full size. Loaded from a specific (hashed) version of the image on GitHub.

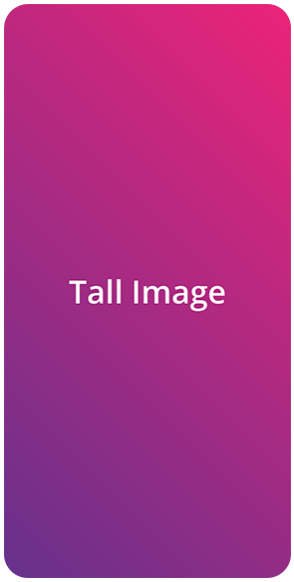

Figure 3: A tall image with a specified height. Loaded from a specific (hashed) version of the image on GitHub.

Figure 4: A vector `.svg` image loaded from GitHub. The parameter `sanitize=true` is necessary to properly load SVGs hosted via GitHub URLs. White background specified to serve as a backdrop for transparent sections of the image. Note that if you want to export to Word (`.docx`), you need to download the image and reference it locally (e.g. `content/images/vector.svg`) instead of using a URL.

Tables

Table 1: A table with a top caption and specified relative column widths.

Bowling Scores	**Jane**	**John**	**Alice**	**Bob**
Game 1	150	187	210	105
Game 2	98	202	197	102
Game 3	123	180	238	134

Table 2: A table too wide to fit within page.

	Digits 1-33	**Digits 34-66**	**Digits 67-99**	**Ref.**
pi	3.14159265358979323 846264338327950	28841971693993751 0582097494459230	78164062862089986 2803482534211706	`piday.org`
e	2.71828182845904523 536028747135266	24977572470936999 5957496696762772	40766303535475945 7138217852516642	`nasa.gov`

Table 3: A table with merged cells using the `attributes` plugin.

	Colors	
Size	**Text Color**	**Background Color**
big	blue	orange
small	black	white

Equations

A LaTeX equation:

$$\int_0^\infty e^{-x^2} dx = \frac{\sqrt{\pi}}{2} \tag{1}$$

An equation too long to fit within page:

$$\begin{aligned} x = a + b + c + d + e + f + g + h + i + j + k + l + m + n + o + p + q + r + s + t \\ + u + v + w + x + y + z + 1 + 2 + 3 + 4 + 5 + 6 + 7 + 8 + 9 \end{aligned} \tag{2}$$

Special

⚠ **WARNING** *The following features are only supported and intended for `.html` and `.pdf` exports. Journals are not likely to support them, and they may not display correctly when converted to other formats such as `.docx`.*

LINK STYLED AS A BUTTON

Adding arbitrary HTML attributes to an element using Pandoc's attribute syntax:

Manubot Manubot Manubot Manubot Manubot. Manubot Manubot Manubot Manubot. Manubot Manubot Manubot. Manubot Manubot. Manubot.

Adding arbitrary HTML attributes to an element with the Manubot `attributes` plugin (more flexible than Pandoc's method in terms of which elements you can add attributes to):

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Available background colors for text, images, code, banners, etc:

`white` `lightgrey` `grey` `darkgrey` `black` `lightred` `lightyellow` `lightgreen` `lightblue` `lightpurple` `red` `orange` `yellow` `green` `blue` `purple`

Using the Font Awesome icon set:

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Light Grey Banner
useful for *general information* - manubot.org

Blue Banner
useful for *important information* - manubot.org

Light Red Banner
useful for *warnings* - manubot.org

References

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   Daniel S Himmelstein, Ariel Rodriguez Romero, Jacob G Levernier, Thomas Anthony Munro, Stephen Reid McLaughlin, Bastian Greshake Tzovaras, Casey S Greene
   eLife (2018-03-01) https://doi.org/ckcj
   DOI: 10.7554/elife.32822 · PMID: 29424689 · PMCID: PMC5832410

2. **Reproducibility of computational workflows is automated using continuous analysis**
   Brett K Beaulieu-Jones, Casey S Greene
   Nature biotechnology (2017-04) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6103790/
   DOI: 10.1038/nbt.3780 · PMID: 28288103 · PMCID: PMC6103790

3. **Bitcoin for the biological literature.**
   Douglas Heaven
   Nature (2019-02) https://www.ncbi.nlm.nih.gov/pubmed/30718888
   DOI: 10.1038/d41586-019-00447-9 · PMID: 30718888

4. **Plan S: Accelerating the transition to full and immediate Open Access to scientific publications**
   cOAlition S
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5. **Open access**
   Peter Suber
   MIT Press (2012)
   ISBN: 9780262517638

6. **Open collaborative writing with Manubot**
   Daniel S Himmelstein, Vincent Rubinetti, David R Slochower, Dongbo Hu, Venkat S Malladi, Casey S Greene, Anthony Gitter
   Manubot (2020-05-25) https://greenelab.github.io/meta-review/

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   Travers Ching, Daniel S Himmelstein, Brett K Beaulieu-Jones, Alexandr A Kalinin, Brian T Do, Gregory P Way, Enrico Ferrero, Paul-Michael Agapow, Michael Zietz, Michael M Hoffman, … Casey S Greene
   Journal of The Royal Society Interface (2018-04) https://doi.org/gddkhn
   DOI: 10.1098/rsif.2017.0387 · PMID: 29618526 · PMCID: PMC5938574

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   Daniel S Himmelstein, Vincent Rubinetti, David R Slochower, Dongbo Hu, Venkat S Malladi, Casey S Greene, Anthony Gitter
   PLOS Computational Biology (2019-06-24) https://doi.org/c7np
   DOI: 10.1371/journal.pcbi.1007128 · PMID: 31233491 · PMCID: PMC6611653