

## ORIGINAL PAPER

ON INTERACTIONS BETWEEN FEVER, INFLAMMATION,  
AND THE AUTONOMIC NERVOUS SYSTEM

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The pathologist Simon Samuel, one of the pioneers in the field of the autonomic nervous system during the 19<sup>th</sup> century, contributed significantly to the understanding of the pathological mechanisms underlying inflammation. The remarkable advances in that field around the mid-19<sup>th</sup> century fundamentally influenced future research of the last 170 years. In fact these findings are still connected with many novel studies on pathology today. Albert Eulenburg (1840–1917) is another scientist who contributed to the former advances in the autonomic nervous system and who closely cooperated with Samuel. Both scientists published articles and reviews in the German journal Schmidt's yearbooks edited by J. A. Winter (1816–1901). It is remarkable that Johann Ignaz Hoppe (1811–1891), an even earlier pioneer of the autonomic nervous system, also wrote articles for the same journal and obviously had influenced Samuel. Although regulations discriminating Jewish academics existed in Prussia (and later in the German Empire) until approximately 1888, Samuel was finally made assistant professor (außerordentlicher Professor) at Königsberg University (today Kaliningrad/Russian Federation) in 1874. An embarrassingly low position compared to the significance of his scientific contributions and to the implications of his work on future generations.

**Key words:** autonomic nervous system, inflammation, 19<sup>th</sup> century history of medicine, Robert Remak, Paul Guttman.

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## Introduction

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Scientific progresses in the field of the autonomic nervous system around the second half of the 19<sup>th</sup> century have to be considered a relevant topic in pathology [1–5]. Today Claude Bernard (1813–1878) and Charles-Édouard Brown-Séquard (1817–1894) are internationally recognized as perhaps the most influential scientists who contributed to that field [2, 4–6]. Nevertheless, several former German-speaking scientists should also be mentioned. Johann Ignaz Hoppe (1811–1891), one of the very first pioneers who especially contributed to pharmacological concepts connected with the autonomic nervous system, published ground-breaking articles during his time

in Prussia and later in Switzerland [7–9]. In the year 1873, Paul Guttman (1834–1893) (born in Rati-bor/Kingdom of Prussia (today Racibórz/Poland)) and Albert Eulenburg (1840–1917) published their remarkable work *Pathology of the sympathetic nervous system on physiological basis* (Physiologie und Pathologie des Sympathicus auf physiologischer Grundlage), which was later awarded the London Medical Society's Astley-Cooper Prize [10–13].

These pioneer scientists were obviously inspired by the early French pathologists and physiologists from the Napoleonic era and their spiritual successors, especially by François Magendie (1783–1855) and Claude Bernard (1813–1878) [10, 14].

### Simon Samuel (1833–1899)

Simon Samuel was born in Glogau/Kingdom of Prussia (today Głogów/Poland) on 5 October 1833 [7]. He began to study medicine at Berlin University in 1851. The brilliant Jewish scientist Robert Remak (1815–1865) (born in Posen/Kingdom of Prussia (today Poznań/Poland)) became Samuel's most important teacher [7]. Although today the concepts of cellular pathology are widely associated with the name Rudolf Virchow (1821–1902), it was in fact R. Remak who proposed some of these concepts earlier [7]. However, many of these ideas might have derived from the Charité Hospital, Pathology Department in Berlin. The influential physiologist Johannes Mueller (1801–1858) and the clinical pathologist Johannes Lucas Schoenlein (1793–1864) were other teachers in Berlin who had a significant influence on Simon Samuel [7]. He continued to study medicine at Vienna University and achieved his doctorate degree at Berlin University in 1855 [7, 15]. Samuel started his medical career as a practitioner in Königsberg/Kingdom of Prussia (today Kaliningrad/Russian Federation) the following year 1856 [7]. He began to publish articles in *Schmidt's yearbooks on the entire field of domestic and foreign medicine* in the year 1860 [2, 16–18]. Therefore, the discussed correspondence from 1 December 1859 obviously marked the beginning of Samuel's scientific career together with the publication of his book on *The trophic nerves (Die trophischen Nerven. Ein Beitrag zur Physiologie und Pathologie)* in 1860 [1]. He achieved his postdoctoral lecture qualification (*Habilitation*) in 1867, after Königsberg University had changed its statutes, which excluded individuals who were not Protestant Christians from postdoctoral lecture qualification [7]. Samuel was promoted to assistant professor for general pathology and therapy (*Professor Extraordinarius*) at Königsberg University in 1874 [7]. Samuel wrote his most significant works on topics which connected inflammation and fever with the autonomic nervous system [1–6, 15, 19–24]. He also published a four-volume textbook on pathology and pathophysiology in 1879 [14]. Therefore, he can be considered as one of the founders of pathophysiology as a subfield of medical science, which had been defined by Rudolf Virchow (1821–1902) [14]. Simon Samuel passed away on 9 May 1899 [7].

### Johann A. Winter (1816–1901)

J. A. Winter, one of the main editors of *Schmidt's yearbooks on the entire field of domestic and foreign medicine* between approximately 1847 and 1900, was born on 20 April 1816 in Leipzig/Saxony [7, 25, 26]. He passed his final medical examination at Leipzig University in 1838 and then, began his career as an assistant at a general practitioner's practice [7, 25].

Simultaneously, J. A. Winter attended medical courses at Leipzig University [25]. He was made an assistant at Leipzig University Hospital in 1840 and achieved his doctorate degree in 1841 [7, 25]. Winter began a long 2-year scientific journey which led him to Berlin, Prague, Vienna, and Paris [7, 25]. Back in Leipzig, J. A. Winter continued his academic career and was made 'assistant professor' (*außerordentlicher Professor*) in 1853 [25]. According to his autobiography, he neither completed an ordinary German postdoctoral lecture qualification, nor did he really specialize in one single field of clinical medicine, which are definitely two remarkable points in connection with Winter's academic career [25].

Furthermore, J. A. Winter successively became an editor of the German journal *Schmidt's yearbooks on the entire field of domestic and foreign medicine* [7, 25]. That was a large-volume journal (approximately 1200 pages each year) which covered the entire field of both theoretical and clinical medicine [27]. However, it faced a successive decline during the 2<sup>nd</sup> half of the 19<sup>th</sup> century, primary because the readers began to prefer more specialized journals [27]. Until approximately 1880, *Schmidt's yearbooks on the entire field of domestic and foreign medicine* still were recognized as a journal of high significance by the majority of physicians [27]. In fact, Winter dedicated approximately 50 years of his life to that journal, which could be considered his true life's work [7, 25, 27]. J. A. Winter passed away in Leipzig on 18 September 1901 [26].

### Material and methods

The main material of this study is Simon Samuel's handwritten correspondence to J. A. Winter from 1 December 1859. It is written on high quality writing paper without watermarks. The sheet of paper (22.1 × 28.3 cm) was folded in half and, as a result, the two pages (front and back) were divided into four pages (two pages (4 and 1) on the front, two pages (2 and 3) on the back; all 22.1 × 14.15 cm), which all contain Samuel's handwriting.

Although the line of provenance could not be completely reconstructed, it was obviously part of J. A. Winter's collection of autographs. We have to consider the possibility that this correspondence might have been alternatively addressed to Winter's co-editor Hermann Eberhard Friedrich Richter (1808–1876) in Dresden [28]. Although Richter formally had lost his professorship around 1849/1850 because of participation in the (failed) democratic revolution (Richter was accused of *high treason (Hochverrat)*); Winter explicitly pointed out in his obituary on H. E. F. Richter that Richter had received a considerable financial compensation (*nicht unerhebliches Wartegeld*) as a civil servant (*Staatsdienst*). Although

he was dismissed from his professorship in 1850, he might have been still addressed with *Dear Professor* (*Hochverehrter Herr Professor*) at least by rather liberal and democratic authors of the journal [28]. Anyway, even in that case it seems plausible that Richter could have later handed over the correspondence to Winter or could have sold the correspondence to his co-editor because it clearly shows similarities to other letters which were part of Winter's former collection. For example, the author's name (*Samuel*) is written on top of page 1 of the cletter together with the year of origin (1859) and the location where the correspondence was written (*Königsberg*) in a characteristic handwriting (maybe it was the handwriting of Winter's daughter who could have sold the single letters after her father's death) [25]. These typical characteristics can be found in many other letters of Winter's collection but not in all of them. The existence of Samuel's articles in Winter's and Richter's journal between approximately 1860 and 1862 is another clear indication of the main material's genuineness [2–6, 16–21, 29–34]. Furthermore, all individuals mentioned in the correspondence could be more or less exactly identified, which also supports the hypothesis that the letter is genuine [7, 35, 36]. The four handwritten pages were compared with other handwritings from different sources and overall, further indications for the genuineness of the discussed correspondence (main material) could be found.

The document analysis method in qualitative research was used in this study. First a German transcript of the correspondence was prepared by identifying each word and each character of the handwritten text. Some of the words were difficult to identify exactly although it was possible to work out the transcript. Successively, the transcript was carefully translated into English. The contents of the correspondence were analysed by comparing them with different independent sources. Step by step, the historical context of the correspondence was highlighted and discussed, resulting in overviews of the topics.

The original material is currently in preparation for archiving in a university archive.

## Results

German transcript of the correspondence from Simon Samuel (1833–1899) to J. A. Winter (or perhaps to his co-editor H. E. F. Richter) with the location and date *Königsberg i./Pr., 1 Dezember 1859* [comments and completions were added in square brackets]:

Hochverehrter Herr Professor!

Mit vielem Dank habe ich Ihr freundliches Schreiben und die mir so bereitwillig gewährten Separatabdrücke empfangen und beeile mich, in Betracht

der angeregten Mitarbeiterschaft, Ihrem Wunsche gemäß, schleunigst zu antworten. Gern bin ich bereit unter den von Ihnen angegebenen Bedingungen über alle deutschen und französischen Werke über Entzündung, Fieber, Nervenphysiologie, experimentelle Pathologie überhaupt, und diesen verwandten Zweigen unserer Wissenschaft zu referieren, resp. zu kritisieren, [next page] auch von Zeit zu Zeit Resümees über diese Fragen zu geben. So präpariere ich Ihnen für den Sommer eine Arbeit über *Zellulärpathologie und die pathologischen Systeme überhaupt* (historisch, kritisch, Feststellung der Tatsachen, Form[ul]ierung [these words were obviously corrected afterwards by Samuel] der Fragen), dann *die Lehre vom Vagus auf ihren gegenwärtigen Standpunkt* und späterhin Ähnliches. Hier steht mir zwar der größte Theil der Zeitschriften zur Disposition, mit oft frühestens nach einem halben, meist erst nach einem ganzen Jahre. Wenn Sie mir die Journalaufsätze im Kreuzformat [perhaps a special method of sending books and journals which could have been used by publishers], mit mehreren Büchern immer zusammen [written in very small characters above the line; the word "gleichzeitig" (simultaneously) was crossed out] schicken wollen, so wie es mit dem Prof. v. Wittich [7] [the physiologist Wilhelm von Wittich (1821–1884) is meant] seitens der Redaktion des Canstatt'schen Jahresberichts ["Canstatt's Jahresbericht über die Fortschritte der gesamten Medicin in allen Ländern", a German journal which was edited by Carl Friedrich Canstatt (1807–1850)] [7] organisiert ist, so sollte ich glauben, daß unser Verkehr weder besonders kostspielig, noch mit irgend welchen Schwierigkeiten verknüpft sein wird. Ihr Verleger Wigand [Otto Wigand (1795–1870)] [35] wird übrigens mit vielen hiesigen Buch Händlern in Verbindung stehen, durch die ebenfalls die Übermittlung von Büchern hin und zurück leicht bewerkstelligt werden kann. Und die Spedition durch Kreuzformat ist ja äußerst billig und [daher (therefore)] wunderte ich mich, daß Sie mir die Separatabdrucke nicht auf diese Weise zukommen ließen.

Wenn nur Ihre Druckseiten nicht so entsetzlich groß wären! Ihr wertgeschätztes Blatt braucht seine Größe wahrlich nicht mehr in so riesigem Format zu suchen.

Indeß stets werde ich alle Kräfte daran setzten, um der Ehre der [next page] Mitarbeiterschaft mich würdig zu zeigen.

Herr Sanitätsrat v. Pastau [Julius von Pastau (1813–1889)] [7] ist nach Berlin übergesiedelt und wenn ich weiß sehe, Frerichs [Friedrich Theodor von Frerichs (1819–1885)] [7] Assistent. Herrn Hartung [most likely the printer, publisher and book trader Hermann Johann Friedrich Hartung (1823–1901) or one of his relatives] [36] werde ich beileben, Ihre Grüße auszurichten.

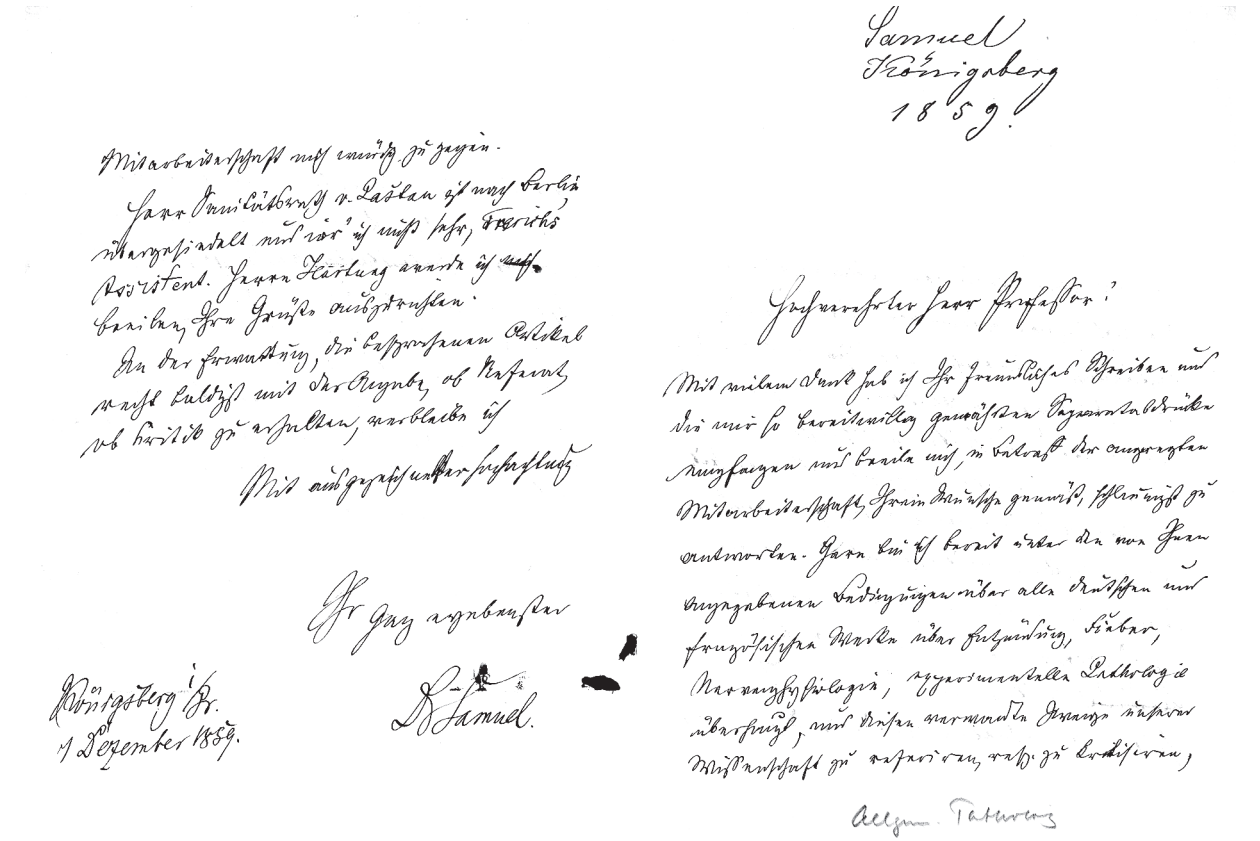


Fig. 1. Front of Samuel's correspondence to J. A. Winter from 1 December 1859 with pages 4 and 1

In der Erwartung, die besprochenen Artikel recht baldigst mit der Angabe, ob Referate, ob Kritik zu erhalten, verbleibe ich

Mit ausgezeichnete Hochachtung  
Ihr ganz ergebenster  
Königsberg i/Pr.  
1 Dezember 1859. Dr Samuel

English translation of the correspondence from Simon Samuel (1833–1899) to J. A. Winter (or perhaps to his co-editor H. E. F. Richter) with the location and date Königsberg i./ Pr., 1 Dezember 1859 [comments were added in square brackets]:

Dear Professor!

I am very grateful for your willingness to send the separate prints and for your friendly letter which I both received [a few days ago]. Therefore, I hurried to answer your letter regarding the suggested collaboration as requested. I confirm that I will be able to write reports and reviews on all German and French works on inflammation, fever, neurophysiology, all topics of experimental physiology, and related fields of [medical] science on these conditions [of the suggested collaboration]. Furthermore, I [will be able to] deliver summaries from time to time. For example, I will prepare a work *On cellular pathology and on the whole field of pathological systems* (historical, critical, establishing the facts, formulation of the ques-

Ihre Ehrenvolle J. A. Winter?

Mit einem dank ich Sie freundlichst bitten und Sie mir so herzlichem gewollten Zuspruch und Anerkennung mit besten Wünschen, in Bezug der angelegten Mitwirkerschaft, Ihnen dankbar zu sein, ich bin sehr dankbar. Ich bin sehr dankbar, dass Sie Ihre Angelegenheiten über alle drücken und freundschaftlichen Worten mir bezeugen, lieber, Maxungshilfen, experimentellen Pathologie überführen, und diese unermesslichen Dienste zu leisten, und diese unermesslichen Dienste zu leisten, und diese unermesslichen Dienste zu leisten.

Allgemeine Pathologie

tions) and on *The theory of the vagal nerve from a current viewpoint*. In future, I could continue to deliver similar articles. [Theoretically,] I have access to most journals here. Although usually, [they are available] half a year later [after publication], in many cases, [it takes] one whole year [after publication until the journal is available]. If you could send the journal articles together with several books in ‘cross format’ [Kreuzformat, perhaps a special method of sending books and journals, which could have been used by publishers], I would think that it wouldn’t be very expensive or connected with any particular difficulties. [It already was] organized in a very similar way with Professor von Wittich [7] by the editors of ‘Canstatt’s [7] Annual Review Journal’. [I would suppose that] your publisher Wigand [35] has contacts with many local booksellers [in Königsberg/Prussia, today Kaliningrad/Russian Federation] who also could easily take on the work of sending and returning the books. The transport with ‘cross format’ is very cheap and [therefore,] I wondered why you didn’t send the separate prints that way.

If only your journal pages wouldn’t be so terribly large! Nowadays your highly regarded journal doesn’t have to rely on such a giant format to emphasize the greatness of its content.

Nevertheless, I will always try everything to preserve the honour of being your journal’s collaborator.



the autonomic nervous system as part of his studies [9]. Furthermore, Hoppe also used frogs for his groundbreaking pharmacological studies on the autonomic nervous system [9].

On the other hand, there are several hints which might suggest that Hoppe rather had a bad reputation among his contemporaries, especially among physicians [37] (“Neue Zürcher Zeitung”, 71<sup>st</sup> volume, issue 261 “zweites Blatt”), from Friday, 18 September 1891, page 2 [a]; see also “Thuner Wochenblatt”, 54<sup>th</sup> volume, issue 94, from Wednesday, 25 November 1891, page 2 [b]). For example, Adolf Kussmaul’s (1822–1902) autobiography states that Hoppe was more or less openly insulted by a colleague to be a madman who performed cruel animal experiments during the 1858, 34<sup>th</sup> *Versammlung Deutscher Naturforscher und Ärzte* in Karlsruhe (a congress of physicians and natural scientists in Germany) [37]. Therefore, Hoppe’s bad reputation could have been the true reason why Samuel and also Eulenburg avoided citing and referring to Hoppe [1, 10, 37].

Taken together, the question on the significance of J. I. Hoppe’s scientific contributions, especially in the field of the autonomic nervous system, urgently needs reconsideration [1, 9, 10, 37]. There are several hints that Hoppe had a very significant influence on different scientific works connected to the autonomic nervous system around the early second half of the 19<sup>th</sup> century, although many of his contemporary colleagues did not cite Hoppe appropriately and did not refer to him [1, 9, 10, 37].

Considering that Hoppe performed many of his relevant animal experiments on frogs and not on mammals and considering that Hoppe’s contemporary colleagues like Claude Bernard also did perform similar animal experiments on mammals, the accusation that Hoppe’s animal experiments would have been especially cruel also appears at least slightly questionable [1, 9, 10, 37].

In the same year 1867, when Samuel achieved his postdoctoral lecture qualification, he also published an article about *Researches on the circulation of the blood in acute inflammation* (Versuche über die Blutzirkulation in der acuten Entzündung) in the influential German journal *Archiv für pathologische Anatomie und Physiologie und für klinische Medizin* (still published under the name Virchows Archiv), formerly edited and released by Rudolf Virchow (1821–1902) [24].

## Conclusions

It is absolutely remarkable that more than 100 years later, in the year 1972, an English translation of this article from 1867 was published in *The American Journal of Cardiology* together with historical comments [38, 39]. This is another hint that the findings of Samuel, Eulenburg, Guttmann, and

Hoppe can be interpreted as important prerequisites for many different future innovations in medicine, e.g. for the discovery of  $\beta$ -blockers’ positive effects on the therapy of heart failure during the following 20<sup>th</sup> century [40].

## Disclosures

1. Institutional review board statement: Not applicable.
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3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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### Articles in newspapers

- a. *Neue Zürcher Zeitung*, under the headlines "Kantone" and "Baselstadt" (left column), 71st volume, issue 261, "zweites Blatt", from Friday, 18th of September, 1891, page 2.
- b. *Thuner Wochenblatt*, next to the headline "Baselstadt" (right column), 54th volume, issue 94, from Wednesday, 25th of November, 1891, page 2.

### Original material

- A. Handwritten letter written by Simon Samuel to J. A. Winter from 1 December 1859. The original material is currently in preparation for archiving in a university archive. At the moment the letter can be inspected at Practice Hohendodeleben, Gartenweg 24, D - 39164 Wanzleben OT Hohendodeleben, Saxony-Anhalt, Germany.

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