

ERENUMAB - (AIMOVIG)



Once upon a time there was a doll's house that belonged to a Queen....a doll's house so marvelously made that from far and near people came to look at it....(illustration, Kate Baylay).

Once upon a time there was a doll's house that belonged to a Queen....a dolls house so marvelously made that from far and near people came to look at it, and wished that, like Alice, they could discover a cake or a bottle, so that they might eat or drink, and grow small enough to walk up the blue and white marble staircase, seat themselves on the throne, pass into the painted bedroom, and bathe themselves in the malachite bath whose silver taps ran hot or cold water at will. But because they lived in London, and not down a rabbit hole, and had paid a shilling to look into the doll's house, and must pass on to allow other people in the queue their turn, they were not able to do any of these enchanting things.

Moreover, peer into the house as they might in consideration of their shilling, being greedy of every second allotted to them, there were some things which they could never see in the house, which nobody had ever seen, or would ever see, not even the maker of the house, although he wore big spectacles, not even the Queen herself, even when she had her crown on, nor even the royal children, though everybody knows that children see a great deal which is hidden from grown-ups. There was for instance, the doll's house ghost, because naturally being a completely appointed house, and all really nice houses being haunted, thick and variously, if only by the vows of love that have been exchanged there (and where they survive unbroken), or by the songs that have been sung there out of happy heart. Perhaps it is not fair to call the doll's house ghost a ghost, for that implies that she was dead, there was never a more lively or inquisitive sprite or one who prided herself more on being up to date.

She had, in fact that particular genius for being in the right place and in the right company at the right moment which under other circumstances would have made of her a conspicuous social success. She was fond of boasting, for instance, that it had been she who had encouraged Jack to set his foot upon the first rung of the Beanstalk and that she had waved Cinderella off to her ball...that one of her most treasured possessions, worn as a locket, was the pea which had given the Princess such a sleepless night, that she had been present when the Prince kissed the Sleeping Beauty, and even - though this was an episode she did not much care to dwell upon - that she had witnessed the death of Bluebeard's first wife. So naturally, with this record behind her, it was only to be expected that she would arrive in London in 1924 to establish herself in the doll's house that had been built for the Queen of England.



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I ought, perhaps to say a word as to her appearance at this date. She prided herself - it was only in keeping with the rest of her principles - on following the fashion of the country and the day; thus when she had gone to lend an ear to Scheherazade (whom she thought long-winded and a bore), she had affected the yashmak, which she thought very becoming, and abandoned with regret. When she was staying with the Marquis of Carabas she had powdered her hair, worn a riding -habit and a tricorne, and had reddened the heels of her shoes; and on her flying visit to China to hear the Emperor's famous Nightingale, which everybody was talking about, she had accommodated herself to the fashions prevalent among the Chinese women, but although she appreciated their skills and their embroideries, she did not care for their style of hair-dressing, and was relieved when the Nightingale was banished from the empire in favour of the new artificial bird, and she was able to return to Europe.

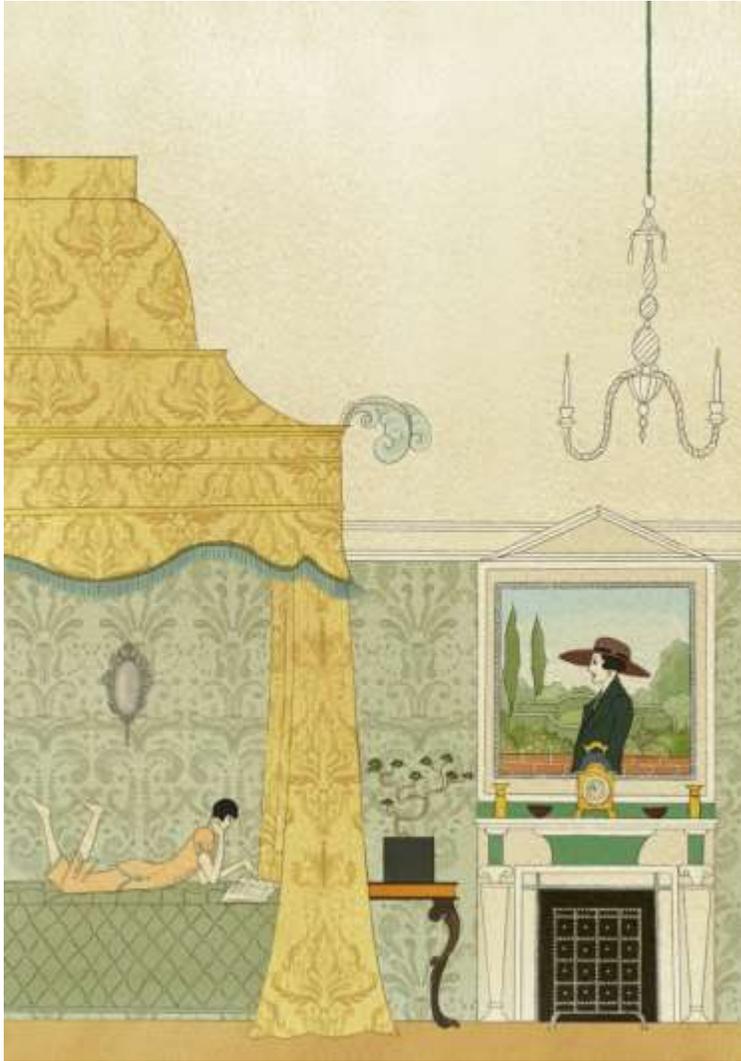


Now in England in the twenties of the twentieth century, she was in two minds as to whether she should or should not bob her hair, but the work of a painter named John (whom she found represented in one of the passages of the doll's house) decided her, and she found herself greatly delighted by the brilliant jerseys and short skirts with which she provided herself for daytime wear, and by her own dark little clubbed head, which gave her a boyish, page-like appearance unfamiliar to her since the ten days she had once spent in listening to the stories of Boccaccio and his friends in a villa above Florence, way back (this was one of her new expressions) in the fourteenth century.

Established in the doll's house, she amused herself by sleeping every night in a different bedroom; indeed, there was no end to her amusements, for she found in the doll's house a great many things she had never seen before and whose use she was obliged to discover for herself. Needless to say, there were at first a few disasters. There was the day when, fully dressed, she brought the shower-bath about her ears; and then there was the day when, going up in the lift, she accidentally touched the "stop" button, and remained stuck between two floors for the rest of the afternoon. But such minor inconveniences were as nothing beside the pleasure which these mechanical contrivances brought her. It must be remembered that all modern inventions were new to her, for she had dallied in the past, and electric light, a hot water system, a kitchen range, and a passenger lift were things which caused her to compare the Aladdin's palace most favorably with the doll's house.

But there was one result of her investigations which has hitherto sorely perplexed the guardians of the doll's house. Every morning on going to take off the coverings and unlock the front, they have found the lights turned on, the baths full, the beds disarranged, the blinds raised where they should have been lowered, the lift upstairs when they were quite sure they had left it on the ground floor overnight, the books pulled out of the shelves, and even on one occasion they found in the dining

room the remains of a meal (for two) and the little silver platters scattered dirty all over the dining-room table. At last they bethought themselves to ask the maker of the house whether he could furnish any explanation, for he was well known for his love of a joke. But though he came and looked at the house in a puzzled way through his biggest pair of spectacles, he finally said no, this was certainly not a joke of his providing!



....she amused herself by sleeping every night in a different bedroom...and then there was the day when, going up in the lift, she accidentally touched the “stop” button....

But now of course, if anybody cares to ruin their eyesight by reading the books in the library, the matter will once and for all be made quite clear, and it is to be hoped that the authorities will cope with this slight difficulty by the simple expedient of supplying a housemaid, and the enigma will once and for all be at an end.

THE END.

Vita Sackville-West, “A Note of Explanation”, 1924.

The most remarkable doll's house ever constructed was built for Queen Mary, the wife of King George V; it was completed in 1924, and today can be seen on display in Windsor Castle. It was the idea of Princess Marie Louise of Schleswig-Holstein who approached the leading architect of the day Sir Edwin Lutyens, at the Royal Academy Summer Exhibition of 1921. Sir Edward enthusiastically agreed to oversee the project and immediately engaged the most talented artists and crafts people of the day.

The doll's house is a 1:12 (i.e. one inch to a foot) exact replica of a real house including all its functioning accoutrements. There are tiny, fully functioning shotguns that "break and load" (and may even fire), monogrammed linens, electric lifts, a garage of cars with engines that run. Water can be made to run through its tiny pipes into a bath and tiny electric chandeliers can be turned on. The wine bottles contain real wine. There is also a garage of exquisite little cars with engines that work. It was a showcase for the very finest and most modern goods of the time, it is, in effect a miniature time capsule. Miniature objects were either made by the companies themselves, or by specialist model-makers, such as Twining Models of Northampton. The carpets, curtains and furnishings are all copies of the real thing, and even the light fittings are working



Most remarkable of all however is the dolls' house library, which contains miniaturized real books each with its own compete story written by famous authors of the time, including. Sir Arthur Conan Doyle, J. M. Barrie, Thomas Hardy, Rudyard Kipling and Somerset Maugham.

Of all the works the most enchanting was recently discovered and published. It is a lost work, or at least a previously unknown work, of Vita Sackville-West, entitled "A Note of Explanation", published for the first time in 2018. It is a delightful children's story that explains the "strange happenings that occur in the doll's house at night". A tiny time traveling sprite (a type of magical fairy), was so enchanted with the doll's house, she decided to move in, comparing it favourably with Aladdin's palace! Each night she would move about the house, exited by all the modern appliances and trying them out, even entertaining her friends in the dining room, and drinking the cellar's wines.

It must be remembered that all modern inventions were new to her, for she had dallied in the past, and electric light, a hot water system, a kitchen range, and a passenger lift were things which caused her to compare Aladdin's palace most favourably with the doll's house....

For decades migraine prophylaxis has been attempted with a vast multitude of drugs - each of totally different class, suggesting a lack of real efficacy of any one of them. To better understand the true intimate inner workings of migraine, however we need a true "Note of Explanation". A tiny mischief making sprite that goes by the name of CPRGR resides within the trigemino-vascular system. By understanding this mischievous sprite we may be better able to control the debilitating symptoms of migraine.

ERENUMAB - (AIMOVIG)

Introduction

Erenumab (trade name “**Aimovig**”) is a novel, first of its kind, **calcitonin gene-related peptide receptor (CGRPR) antagonist**, used for the **prophylaxis** of **migraine headache** in adults.

Despite the traditional availability of a range of (supposedly) oral preventive therapies for migraine, patients often discontinue treatment due to **lack of efficacy** and/ or poor tolerability.³

Moreover, most of the drugs used in preventive treatment of migraine were initially designed for other purposes, reflecting the need for newer **migraine-specific** therapeutic agents.

Calcitonin gene-related peptide (CGRP) is a neuropeptide implicated in migraine pathophysiology. Ample clinical evidence shows that CGRP and the CGRP receptor are suitable targets for the acute and preventive treatment of migraine. **Erenumab** is a fully human monoclonal antibody that targets and blocks the CGRP receptor.

Erenumab is available as a single use **pre-filled autoinjector**, intended for patient self-administration or as a single use **pre-filled syringe**.

It is taken as a **once a month** injection

Erenumab can significantly reduce the average number of migraine days over a month in *some* migraine sufferers.

Many patients experience a reduction of monthly migraine days to at least 50%.

It can also be effective in more difficult to treat populations.

History

Erenumab is the first CGRPR antagonist to be approved for clinical use.

The US Food and Drug Administration (FDA) has approved erenumab for the preventive treatment of migraine in adults in May, 2018.

Chemistry

Erenumab-aooe is a human immunoglobulin G2 (IgG2) **monoclonal antibody** that has high affinity binding to the **calcitonin gene-related peptide receptor**.

It is produced using recombinant DNA technology.

Physiology

Calcitonin gene-related peptide (CGRP) is a **neuropeptide**. It is a member of the *calcitonin family* of peptides, which in humans exists in two forms, α -CGRP and β -CGRP.

GCRP plays a key role migraine pathophysiology

CGRP is:

1. A potent dilator of cerebral blood vessels.
2. Involved in the transmission of nociception

In the trigemino-vascular system, cell bodies in the trigeminal nerve ganglia constitute the **main source** of CGRP.

Activation of the trigeminal nerve causes CGRP to be released from perivascular nerve endings.

CGRP acts on the CGRP receptor to cause vasodilation of cerebral blood vessels

CGRP levels have been shown to increase significantly during migraine and return to normal with headache relief.

Classification

Erenumab is a novel, first of its kind, **calcitonin gene-related peptide receptor (CGRPR) antagonist**

Preparations

Erenumab comes in 2 different types of devices:

Erenumab as:

A single-dose pre-filled autoinjector, syringe:

- 70 mg/mL solution

A single-dose (1 time) pre-filled syringe:

- 70 mg/mL solution

The syringes must be kept in a refrigerator, between **2 - 8 degrees Celsius**.

They must not be allowed to freeze.

They may be stored at room temperature (i.e up to **25 degrees Celsius**) for up to **7 days** after removing it from the refrigerator, but must be *discarded after this time*.

Novartis currently produces Erenumab as “**Erenumab - aooe**”. Note that the “aooe” designation is merely an FDA specific code to distinguish “biosimilars”, and implies no specific pharmacological action or activity.

Mechanism of Action

Calcitonin gene related peptide (CGRP) is involved in the pathophysiological mechanisms underlying migraine through **nociceptive** mechanisms within the **trigemino-vascular system**.

Erenumab-aooe is a human immunoglobulin G2 (IgG2) monoclonal antibody that has **high affinity binding** to the **calcitonin gene-related peptide receptor**.

Erenumab therefore **blocks the function** of the **CGRP receptor** and so prevents cerebral blood vessel vasodilation - and hence helps to prevent migraine headache.

Pharmacodynamics

Erenumab can significantly reduce the average number of migraine days over a month in *some* migraine sufferers.

Many patients experience a reduction of monthly migraine days to at least 50%.

It can also be effective in more difficult to treat populations.

The **long-term** safety and durability of the effect of erenumab will require further study.

Pharmacokinetics

Absorption:

- Erenumab is administered by SC injection.
- The estimated absolute bioavailability of erenumab is around 80 % following a single SC dose of 70 or 140 mg in healthy adults.

Distribution

- The mean Vd of erenumab has been estimated at 7.6 L following a single 140 mg *IV* dose. This suggests limited tissue distribution outside of plasma.
- It is unknown if erenumab crosses the human placenta.
- It is unknown if erenumab is excreted into human breast milk.

Metabolism and excretion:

- At low concentrations, the elimination of erenumab is mostly through saturable binding to target calcitonin gene-related peptide receptor.

At higher concentrations the elimination is mostly through a non-specific, non-saturable proteolytic pathway.

Indications

Erenumab is used for the **prophylaxis** of **migraine headache** in **adults**

Contra-indications/precautions

These include:

1. Patients with latex allergies, (see below).
2. Safety and effectiveness in pediatric patients have not been established

Pregnancy

There is no adequate data on the developmental risk associated with the use of erenumab in pregnant women.

Animal studies, however, have not to date, shown any adverse effects, in regards to pregnancy.

Breast feeding

There is no data on the presence of erenumab in human milk, the effects on the breastfed infant, or the effects on milk production.

Adverse Effects

1. Local injection site reactions, mainly:
 - Pain
 - Erythema
 - Pruritus.
2. Hypersensitivity reactions:
 - Rash
 - Swelling/oedema.
3. Latex allergy reactions:
 - The needle shield within the white cap of the pre-filled autoinjector and the gray needle cap of the prefilled syringe contain dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals **sensitive to latex**
4. Development of antibodies:

- As with all therapeutic proteins, there is potential for immunogenicity, including the development of neutralizing antibodies; i.e. neutralizing anti-erenumab antibodies.

5. GIT upset:

- Constipation most commonly.

Dosing

The recommended adult dosage is **70 mg SC, once monthly**.

Some patients may require a dosage of **140 mg SC, once monthly**

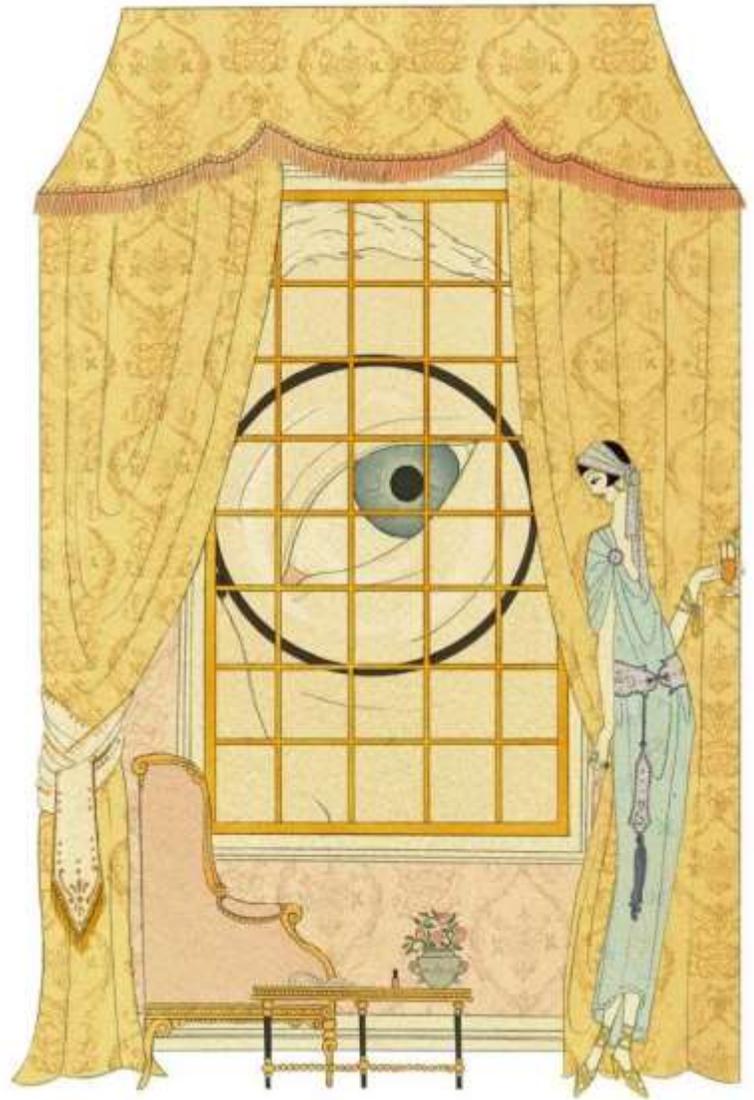
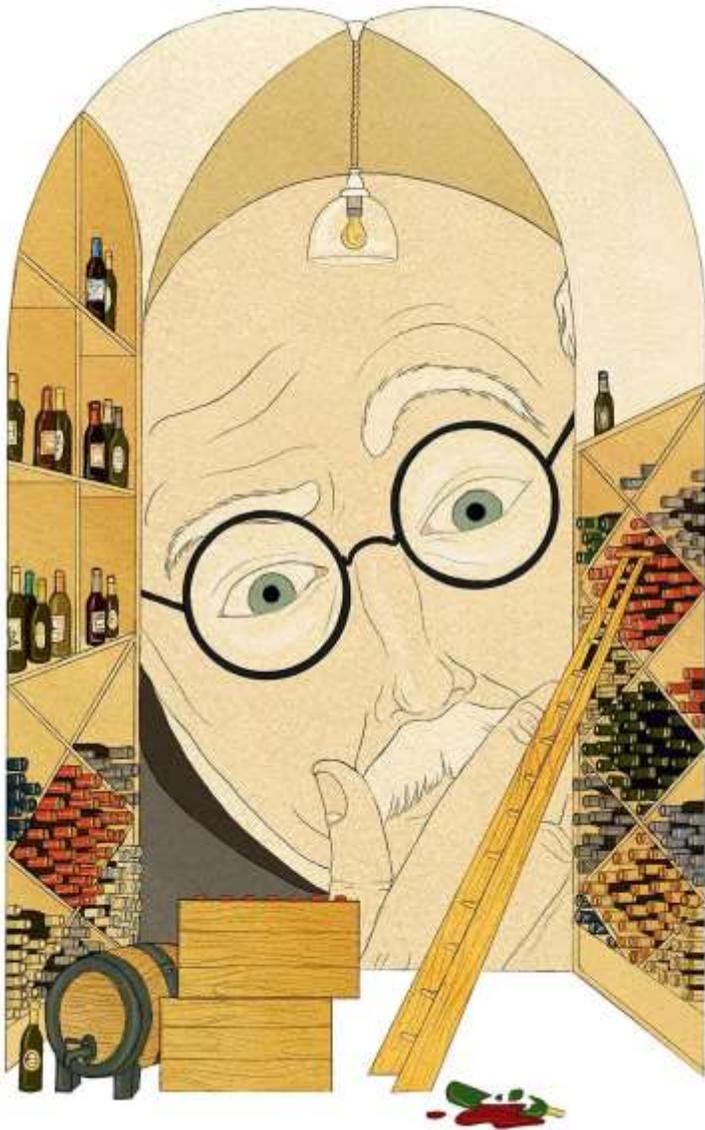
The 140 mg dose is administered once monthly as **two consecutive injections** of 70 mg each

Allow the pre-filled syringe to come room temperature for at least **30 minutes** protected from direct sunlight. Do not warm the syringe by using a heat source such as hot water or a microwave.

Do not shake the product.

It is administered in the **abdomen, thigh, or upper arm** subcutaneously.

The need for treatment continuation should be re-evaluated within regular intervals of 3 - 6 months as recommended by the current treatment guidelines.

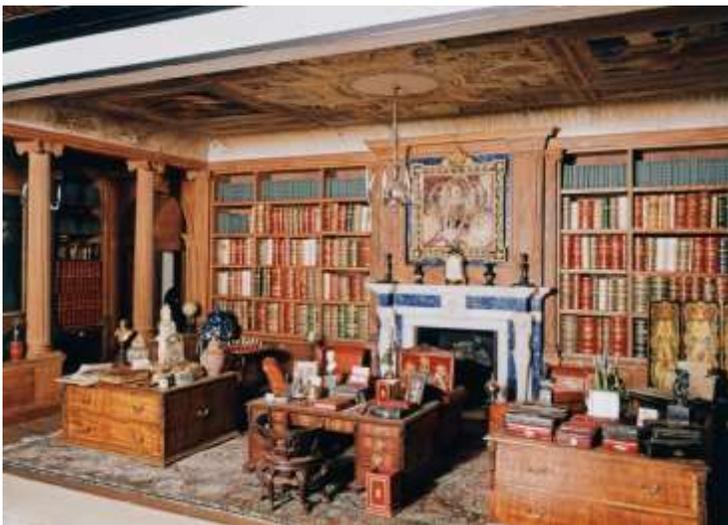


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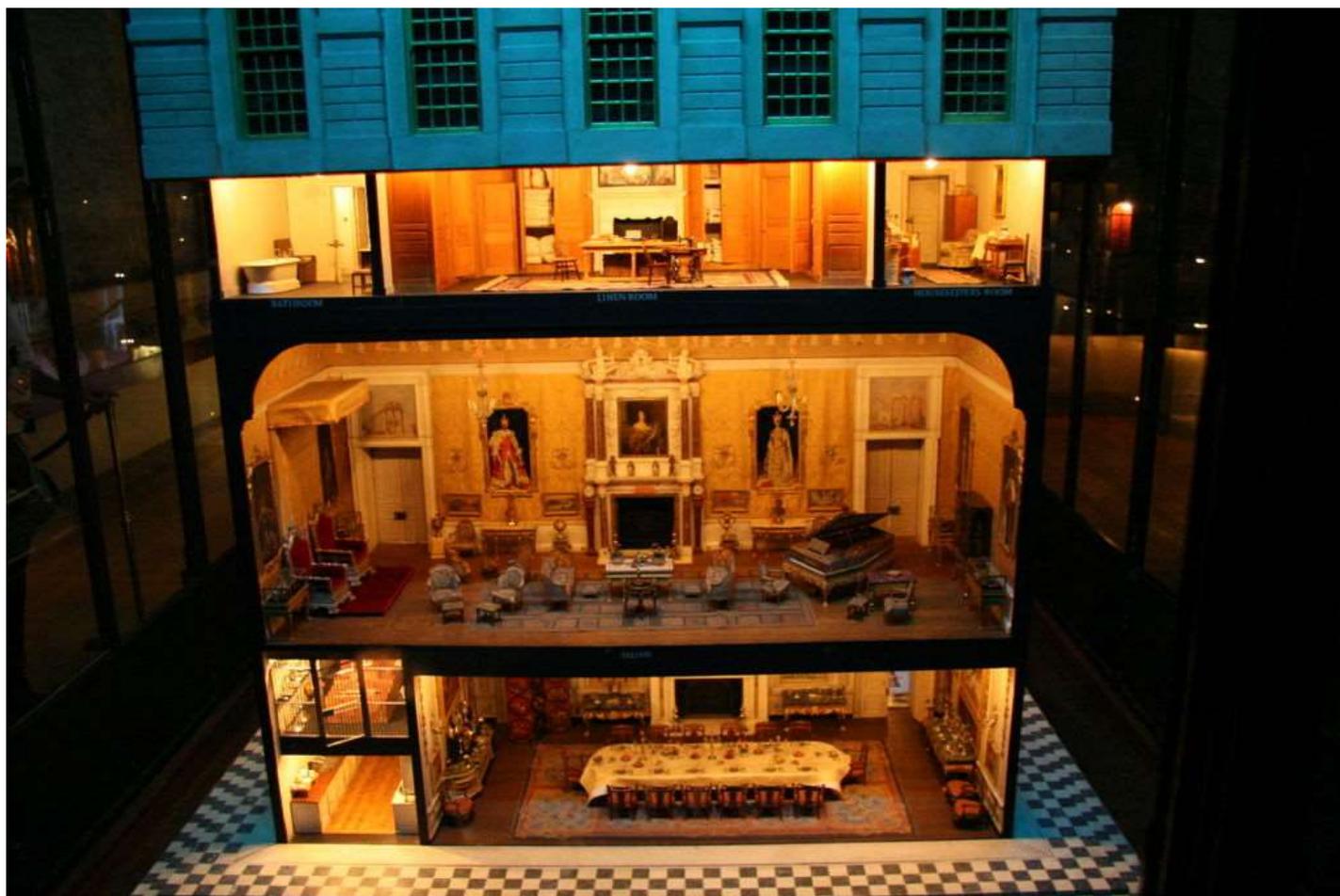


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Above: A book from the library of Queen Mary's Doll's House.

Left: The Library of Queen Mary's Doll's House. Right: "A Note of Explanation", by Vita Sackville-West.



Above: Queen Mary's Dolls House at Windsor today. Below left: Being constructed in the early 1920s. Below right: Vita Sackville-West, c. 1924

References

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Dr J. Hayes

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