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Prussian Blue: From Accidental Pigment to Diagnostic Gold Standard

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Abstract

Prussian blue has crossed a variety of disciplines. Prussian blue was found by chance in Berlin at the beginning of the eighteenth century, and was then the first synthetic dye used on a large scale, leading to a revolution in artistic expression throughout Europe and Asia. It was deep in color and stable, which changed the way paintings, printmaking, and textiles were made, and in time influenced some of the greatest artworks of all time. The pigment was used in medicine as well as art. Max Perls, in 1867, modified the chemistry of Prussian blue to make it suitable as a stain for tissues for ferric iron, which is one of the longest-lasting stains used in diagnostic pathology. Perls' Prussian blue stain is an essential part of the evaluation of iron overload disorders, pulmonary hemosiderosis, myelodysplastic syndromes, and forensic work today. Incredibly, Prussian blue is also an FDA approved therapeutic agent for radioactive cesium and thallium poisoning. Prussian blue's development from an accidental laboratory contaminant, a scientific curiosity, and an antidote is a testament to how one molecule can have a lasting impact on human knowledge through serendipity, curiosity, and interdisciplinary innovations. The review provides an overview of the history and chemical basis, pathological uses, forensic importance, therapeutic uses, and future potential of Prussian blue.

Keywords: Prussian blue, Perl's stain, hemosiderin, iron histochemistry, pathology, art history, iron overload, forensic pathology.

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INTRODUCTION

History of science has been marked with discoveries made by accident rather than by careful experiments. One of the most significant of these was the accidental discovery of Prussian blue, a pigment that was not only the first modern synthetic pigment, but also had a profound impact on art practice in Europe and Asia as a whole [1].

But its significance goes beyond just looks. One hundred years later, the same chemical reaction used to create the pigment was used by Max Perls to detect ferric iron in biological tissues [2]. As a result, the 'Prussian blue' stain is one of the oldest and most reliable in routine histochemistry.

Although there has been a significant advancement in molecular diagnostics, digital pathology and artificial intelligence supported microscopy, Perl's staining remains a crucial tool in the diagnostic workflow as it is the only method that directly visualizes the deposition of iron within its anatomical context. The capacity to direct iron to certain cells, tissues, and compartments, which cannot be completely captured by biochemical or genetic testing, offers valuable information.

This review traces the incredible development of Prussian blue from its accidental genesis in the 1700s, while Prussian Berlin was in existence, to its use in pathology, forensic science, and therapeutic medicine today.

Historical Discovery of Prussian blue

The discovery of Prussian blue is usually dated to 1704-1706 when the pigment maker Johann Jacob Diesbach discovered it in Berlin [1, 3]. When Diesbach was trying to make a red lake dye from extracts of

cochineal, he had used potash that had been contaminated with animal residues from the alchemist Johann Konrad Dippel's laboratory [3].

The reaction should give rise to a red coloured precipitate, but instead, a dark blue colour precipitate was formed. Neither Diesbach nor Dippel knew exactly what they were adding, but cyanide-containing compounds and iron were added, leading to the production of ferric ferrocyanide, or Prussian blue [3, 4].

This finding was a turning point in the technology of pigments. Before Prussian blue was available, artists used mostly ultramarine blue, which was made from the mineral lapis lazuli from Afghanistan. Due to the scarcity and price, ultramarine was often more expensive than gold [5]. This meant that it was difficult to obtain good quality blue, and so it was strictly for the rich patrons and large orders.

The importance of this new pigment was immediately realised by Johann Leonhard Frisch, who encouraged its commercial manufacture. Prussian blue was scientifically described by its name in 1710 and began to be produced on a large scale [1]. In the next few decades, the pigment became available all over Europe and beyond, making it much more affordable to get that deep blue hue.

Prussian blue is widely considered to be one of the first industrial chemical applications to have an impact on the world of art and culture, and the birth of the modern synthetic chemistry of pigments [4].

Prussian blue and the Transformation of Art

Prussian blue was a game-changer in art. The new pigment was not as expensive as ultramarine, chemically stable and could yield deep navy blue to light azure colours [5].

Prussian blue was a popular pigment in the paintings of the artists of Europe during the 18th and 19th centuries. It was featured in the works of such artists as Jean-Baptiste Lemoyne, Thomas Gainsborough, Vincent van Gogh, Pablo Picasso, and many others [5,6].

Its impact on the world was most vividly felt since its importation into Japan via the Dutch trading networks during the late Edo period. Before Prussian blue came along, Japanese artists used predominantly indigo dyes, which were not as saturated and permanent as Prussian blue [6]. This use of Prussian blue led to the development of the art movement called aizuri-e or "blue prints." Katsushika Hokusai's Thirty-Six Views of Mount Fuji (1830-1832) is the most famous, with the iconic Under the Wave off Kanagawa ("The Great Wave") [6] being the most popular.

The prints then inspired other European Impressionist and Post-Impressionist artists, which came to be known as Japonisme. So Prussian blue made an extraordinary cultural trip: it was invented in Europe, turned into something in Japan and then it came back and influenced European art again [6]. Few pigments in history have exerted such a widespread and lasting artistic impact.

Chemical Structure and Properties

Prussian blue is a mixed-valence coordination polymer composed primarily of ferric and ferrous iron linked through cyanide bridges [4]. Its idealized chemical formula is:

Fe_{4}[Fe(CN){6}]{3}\cdot xH_{2}O

The strong blue colour is due to intervalence charge transfer between Fe2+ and Fe3+ ions of the crystal lattice [4].

The pigment is very insoluble, chemically stable and under most circumstances resistant to photodegradation. The properties account for its usefulness in art and for its use in histochemistry. Modern investigations have shown that Prussian blue has a complicated crystal structure that has varying degrees of hydration, lattice vacancies or mixed oxidation states [4]. It has special optical and ion exchange properties due to these structural features.

Curiously, the same physicochemical properties are responsible of its current medicinal applications application as a decorporation agent of radioactive isotopes [7].

Max Perls and the Birth of Iron Histochemistry

Since its discovery, Prussian blue was used mainly as a pigment by artists for over one and a half centuries. The evolution of its use as a diagnostic tool started in 1867 when the German pathologist Max Perls tried to differentiate iron-containing pigments from melanin and other brown intracellular deposits [2].

Pathologists at the time often saw deposits of pigmented granules in tissue, but had few reliable ways to determine the composition of the granules.

Perls discovered a reaction between potassium ferrocyanide and hydrochloric acid. The hemosiderin has been reduced to Fe++ which then reacts with ferrocyanide ions to produce Prussian blue directly in the tissue section [2, 4].

The reaction can be summarized as:

$$\mathbf{Fe^{3+} + K_4\,[Fe(CN)_6] \rightarrow Fe_4[Fe(CN)_6]_3}$$

Ferric ions are released from storage iron complexes (such as hemosiderin) in the presence of hydrochloric acid. Ferrous iron is then released which can react with ferrocyanide to form the characteristic blue precipitate [2].

Importantly, heme-bound iron is not available under these reaction conditions, explaining the specificity of the stain for storage iron and not whole erythrocytes [4].

Perl's' innovation transformed iron from an invisible biochemical entity into a directly observable histological feature.

Diagnostic Applications in Modern Pathology

Hepatic Iron Overload

One of the biggest modern use of Perl's staining is to measure the amount of iron in the liver [8].

Iron overload can be caused by:

- Hereditary hemochromatosis
- Secondary hemosiderosis
- Chronic transfusion therapy
- Chronic liver disease
- Alcohol-associated liver injury
- Metabolic dysfunction-associated steatotic liver disease

Perls staining allows the determination of the amount and distribution of iron. Common diagnostic clues are often the pattern of deposition. Inherited hemochromatosis is indicated by the cellular predominance of iron in the liver and transfusional iron overload is indicated by the accumulation of iron in the reticuloendothelial cells [8].

Tissue staining can identify the spatial localization and compartmentalization of iron deposition in contrast to serum ferritin measurements.

Bone Marrow Examination

Perls stain is essential for bone marrow disease. The stain is regularly applied to assess marrow iron stores and detect ring sideroblasts in MDS [9]. Ring sideroblasts are abnormal erythroid precursors with abnormal perinuclear iron deposits in the form of mitochondria. They are important to identify in the diagnosis of sideroblastic anemia and specific molecular subtypes of myelodysplastic neoplasms [9].

Pulmonary Pathology

Pulmonopathy: Perls staining is used to identify hemosiderin-laden macrophages in the following conditions:

- Pulmonary hemorrhage
- Diffuse alveolar damage
- Mitral stenosis
- Pulmonary venous hypertension
- Idiopathic pulmonary hemosiderosis

The stain also shows ferruginous bodies in asbestos lung disease, which helps in diagnosis of the occupational lung disease [10].

Renal Pathology

Perls staining is useful for diagnosis of hemosiderin deposits in the renal tubular epithelial cells, especially in chronic intravascular hemolysis [11].

Renal hemosiderosis may be a sign of hemoglobinuria which can occur with paroxysmal nocturnal hemoglobinuria or mechanical hemolysis.

Neuropathology

Iron dysregulation is involved in the etiology of several neurodegenerative diseases such as:

- Parkinson disease
- Alzheimer disease
- Neurodegeneration with brain iron accumulation (NBIA)

Advanced imaging techniques are increasingly using iron deposition in the brain, but the role of histochemical iron detection in neuropathological studies remains.

Forensic Applications

Perls staining has an important role in forensic pathology. It is one of the most commonly accepted uses is the assessment of hemorrhage age. After bleeding, macrophages progressively remove erythrocytes, while accumulating hemosiderin. Iron deposition is usually evident a few days following injury [4].

The timing of occurrence is debatable but the presence of hemosiderin-laden macrophages can help with estimates of chronicity of hemorrhage [13].

The stain has been found to be useful in:

- Subdural hematomas
- Soft tissue injuries
- Contusions
- Chronic pulmonary hemorrhage

In gunshot residue analysis, Prussian blue staining can be used to show the transfer of iron particles to the clothing of gunshot victims and "rust ring" formation [14].

Likewise, the release of metallic iron into neighbouring tissues following a button battery injury allows the histochemical detection of iron deposition in the surrounding area [14].

In combination with other immunohistochemical stains (glycophorin A), Perls staining provides important clues to the vitality of the wound and the timing of the bleeding.

Prussian Blue as a Therapeutic Agent

One of the most amazing evolutions of Prussian blue has been its use as a medicine. The U.S. Food and Drug Administration has approved oral Prussian blue (Radiogardase®) for use in treating internal

contamination with radioactive cesium and thallium in 2003. The drug works by blocking the reabsorption of these ions within the gut and increasing the elimination of the ions in the faeces, thus preventing the enterohepatic recirculation. The U.S. Food and Drug Administration (FDA)

There have been significant decreases in the biological half-life of radioactive contaminants observed clinically after administration of Prussian blue. Crystal lattice of the compound acts as an ion exchange matrix with strong cesium and thallium ion affinity. (Drugs.com)

The mechanism could be represented by:
The binding of cesium/thallium in the intestinal lumen

- Prevention of reabsorption
- Enhanced fecal elimination
- Lowered radiation doses to tissues

Internationally, Prussian blue is still kept in stock for use in radiological emergencies and nuclear incidents. (U.S. Food and Drug Administration). So, a pigment accidentally discovered in 18th century Berlin is today becoming an antidote to radiological poisoning.

Emerging Applications and Future Directions

There are indications that there is much more to the scientific tale of Prussian blue than meets the eye.

Studies on Prussian blue analogues have led to suggestions for their use in:

- Nanomedicine
- Drug delivery systems
- Biosensors
- Magnetic materials
- Energy storage devices
- Electrochromic technologies

Nanoparticle formulations of Prussian blue are under investigation for targeting drugs to tumors, imaging tumor cells, and photothermal therapy [15]. Digital image analysis is also combined with Perls staining in pathology to allow for objective measurement of the amount of iron present in tissue and reduce observer variability and improve reproduction.

The use of artificial intelligence (AI) with histopathology platforms could potentially further improve the diagnostic utility of iron staining by incorporating spatial iron maps with genomic and clinical information.

The development indicates that Prussian blue could be a platform technology to continue to grow from a historical pigment in the field of medicine and materials science.

CONCLUSION

Prussian blue has a fascinating story, and one of accident, artistry, chemistry, and medicine. It was a blue pigment invented in the 18th century in an unsterile reagent in a Berlin workshop, and it changed art practice as it revolutionized the creation of blue in an affordable, reliable synthetic. It had an impact on European portraiture; Japanese woodblock prints and eventually back again to Europe via Japonisme.

More important to medicine, the chemistry of the pigment gave the impetus to the development of one of the most enduring stains used in pathology, Max Perl's stain. Over 150 years since its inception, ' Prussian blue stain' is still the benchmark for the diagnosis of storage iron in tissue and is still used to guide the diagnosis of iron overload disorders, hematologic diseases, pulmonary pathology, and forensic investigation.

An extra chapter was added to the story when the Prussian blue was approved by FDA as a therapeutic medicine to treat radioactive cesium and thallium contamination. There are few compounds that can boast of their impact on artistic history, their influence on pathological diagnosis, and their role as life-saving antidote.

Each time a pathologist sees blue hemosiderin granules on a stained slide he or she follows a 300-year line of scientific history from an accident in Berlin to the contemporary diagnostic laboratory.

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