A Picture is Worth a Thousand Words: Art and Medicine

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ABSTRACT: Medical practice is a form of art, with each complex detail essential to the welfare of the individuals in the care of the physician. Art and medicine have shared a close relationship in a variety of ways for centuries, as demonstrated by anatomical drawings and textbooks from the 16th century. Leonardo da Vinci, driven by his fascination with the details of the human body and how it functioned, succeeded in creating an anatomical model of the cerebral ventricles and the aorta using molten wax and a glass structure, respectively (*Heart and its Blood Vessels*). By using water that contained grass seeds, this experiment enabled him to study blood flow. da Vinci's engrossment with the complexity of the human body is reflected in many of his drawings, including the famous depiction of the human physique in his drawing of the *Vitruvian Man*. This drawing, which defines the ideal proportions of the human body and their correlation with geometry, is an example of how artistic and scientific objectives integrate with each other.

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In this review, we present several cases demonstrating the importance of the art of observation. We believe these cases emphasize how the intersection of medical science with art and the humanities may provide important clues for physicians attempting to resolve complex medical questions [1,2]. Leonardo da Vinci, with *Heart and Its Blood Vessels* [Figure 1] and *Vitruvian Man* [Figure 2], shows one artist's rendition of human anatomy.

THROUGH A YELLOW FILTER

Vincent van Gogh (1853–1890) is one of the most famous, gifted, and creative artists of all time. However, the neuropsychiatric illnesses he experienced, which afflicted him almost all of his life, still remain a mystery. Several organic diseases and various psychological disorders have been attributed to van Gogh. These include psychiatric disorders such as schizophrenia and bipolar disorder, as well as epilepsy, chronic absinthe intoxication, Ménière's disease, syphilis, gonorrhea, and acute intermittent porphyria [3]. All these conditions have been considered possible diagnoses for his various symptoms including dyspepsia, nightmares, mood instability, self-mutilation, seizures, anxiety, hallucinations, insomnia, and impotence, which he describes in his letters [4].

Medical practice is a form of art, with each complex detail essential to the welfare of the individuals in the care as physicians

van Gogh was treated by his physician for his presumed neuropsychiatric diseases with digitalis, extracted from the purple foxglove plant [5]. In the 19th century, digitalis was considered one of the treatments for epilepsy as well as for some psychiatric illnesses [6]. It was used as a sedative, an anticonvulsant, and an anti-manic agent. One of the well-known side effects of systemic digitalis treatment is a disturbance in yellow-blue vision (xanthopsia) [7], similar to viewing the world through a yellow filter. An additional visual side effect may be experienced as glare and colored haloes. Many of van Gogh's artistic works have a definite yellow cast, for example, *The Starry Night*, *The Night Café*, and *Sunflowers* [Figure 3]. Later self-portraits all have a distinctive yellow hue. The yellow tone in his painting is especially noticeable in the work *Enclosed Field with Reaper* (Figure 3D]. It is possible that due to digitalis-induced xanthopsia, van Gogh perceived the world with a yellow tint, which also resulted in the predominance of colored haloes around light sources in some of his works [8-11].

Interestingly, on the only two occasions when van Gogh painted his physician, Dr. Paul-Ferdinand Gachet was holding a foxglove plant. One of the more popular historical stories behind digitalis revolves around the painting *The Portrait of Dr. Gachet* [Figure 4]. Whether this foxglove plant was van Gogh's way of telling us that he suffered from the effects of digitalis poisoning at Dr. Gachet's hand, or that it was simply a symbol of medicine itself, is still a matter of debate [5,9,10,12].

Alternatively, it has been proposed that the haloes in the works of van Gogh are due to a form of glaucoma. The elevation in intraocular pressure associated with glaucoma can lead to corneal edema [13]. The swollen cornea diffracts light into its component parts, causing the observer to perceive colored haloes around light sources. However, since glaucoma is rarely seen among individuals under the age of 40, it is unlikely that van Gogh, who died at age 37, was so affected. It is possible, however unlikely, that the profusion of yellow in the art of van Gogh is simply part of his artistic style. Nonetheless, xanthopsia induced by digitalis provides an interesting hypothesis to

Figure 1. *Heart and its Blood Vessels*, Leonardo da Vinci, second half of the 15th century, Biblioteca Ambrosiana, Milan, Italy

Figure 2. *Vitruvian Man*, Leonardo da Vinci, 1490, Gallerie dell'Accademia, Venice

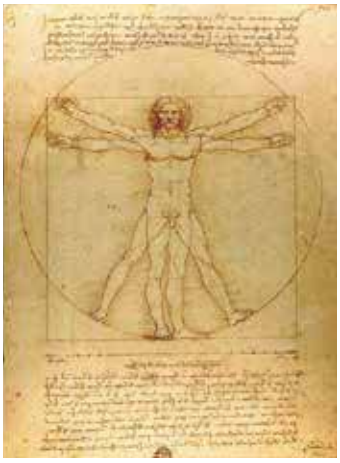


Figure 3. The yellow cast in the artistic works of Vincent van Gogh: **[A]** *The Starry Night*, 1889, Museum of Modern Art, New York City **[B]** *The Night Café*, 1888, Yale University Art Gallery **[C]** *Sunflowers*, 1887, National Gallery, London, England **[D]** *Enclosed Field with Reaper*, 1889, Kröller-Müller Museum, Otterlo, the Netherlands

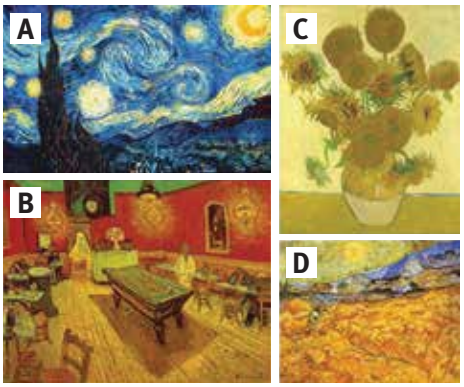


Figure 4. *Portrait of Dr Gachet*, Vincent van Gogh, 1890; oil on canvas, 67×56 cm, private collection

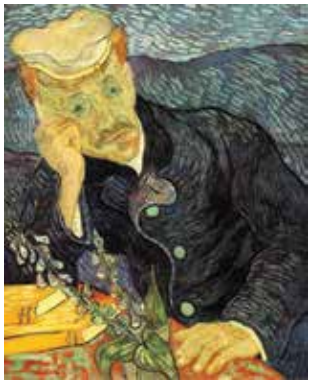
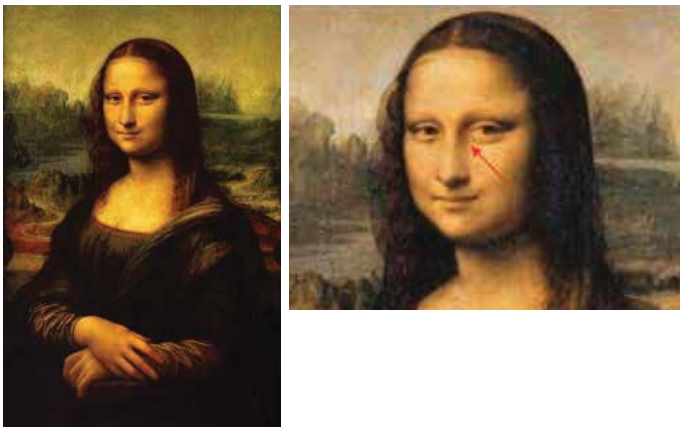


Figure 5. *Holy Virgin with Canon*, Jan van Eyck, 1436, Groeninge Museum, Bruges, Belgium

Figure 6. *Mona Lisa* (La Gioconda), Leonardo da Vinci, 1503, Louvre, Paris



account for the predominance of yellow in the various works of van Gogh.

IN THE EYE OF THE BEHOLDER

Another painting discussed extensively in terms of medical conditions is the work of Jan van Eyck depicting the *Holy Virgin with Canon* (1436), with the Canon providing the medical interest [Figure 5]. This painting is housed in the municipal museum of Bruges, Belgium. In 1981, Dequeker [14] described the appearance of the Canon's prominent left temporal arteries, along with scar formation and hair loss in this area, a characteristic picture of temporal arteritis. The Canon's left arm, diffusely swollen, may indicate longstanding shoulder pain and stiffness, a feature of polymyalgia rheumatica. Historical documents cited by Dequeker in his article further confirm this presumed diagnosis, indicating that around the age of 50 the Canon first began to experience difficulty attending the morning service. The Canon died 12 years later–a history compatible with the natural course of polymyalgia rheumatica [15]. Although temporal arteritis was first described in 1932 by Horton et al. [16], and its association with polymyalgia rheumatica not until 1964 by Hamrin and colleagues [17], it seems that these diseases are not limited to modern times and have existed for many years.

Art and medicine have shared a close relationship in a variety of ways for centuries, as demonstrated in the works of van Gogh, Michelangelo, Goya, and others

THE *MONA LISA*: YOU CAN TELL BY THE WAY SHE SMILES

A careful clinical examination of the famous painting *Mona Lisa* by Leonardo da Vinci [Figure 6] reveals a yellow, irregular plaque in the medial aspect of her left upper eyelid, consistent with xanthelasma, as was described by Dequeker and co-authors [18].

Xanthelasma, most often occurring in middle-aged and older adults, is characterized by cholesterol-filled eyelid lesions, a classic feature of hyperlipidemia. It is estimated that hyperlipidemia is present in approximately 50 percent of patients with xanthelasma [19,20]. Xanthelasma is common in primary biliary cholangitis, a condition often associated with marked hypercholesterolemia, as well as in primary disorders of lipid metabolism and in familial hypercholesterolemia [21]. The importance of evaluating for secondary causes is unclear. The investigators performed a chart review of new patients referred to the University of Michigan Lipid Clinic from January 2004 to June 2011 (n=824).

Thus, an observation of a xanthelasma in the eye region of a woman aged 25–30 years may suggest that Mona Lisa suffered from familial hyperlipidemia, which might have been the cause of her death in 1516 at the age of 37.

In addition to her eyelid, the enigma of the Mona Lisa smile has been extensively studied in terms of medical applications. Adour [22] suggested that Mona Lisa had a facial muscle contracture rather than a smile, with Bell's palsy being the most likely pathogenic cause, causing partial wallerian degeneration. Borkowski [23], however, proposed that it is a facial expression due to the loss of her front teeth. The "Mona Lisa syndrome" will remain a subject of conjecture, but it is a classic example of Leonardo da Vinci as the compulsive anatomist who combined art and science.

The observation of artwork may enhance certain skills physicians need to understand a complex medical problem, such as searching for clues beyond science, demonstrating the integration of medical science with art

GOUT OR NOT GOUT?

The artist Michelangelo Buonarroti (1475–1564) was an Italian master anatomist, painter, sculptor, poet, and engineer who lived during the Renaissance period. The joint disease that afflicted this brilliant artist has been a matter of debate in the medical literature for over a decade. In 1999, Espinel [24] was the first to claim that Michelangelo suffered from gouty arthritis, based on the appearance of his knee in Raphael's fresco at the Vatican, *The School of Athens* [Figure 7]. When examining this portrait of Michelangelo, one can notice an enlarged and deformed right knee. The knee shows no clear signs of joint inflammation; the skin looks pale and tense, rather than red and hot. Nevertheless, there is evidence of several tophaceous deposits located above and below the patella and over the bursa. In addition, in the *Letters of Michelangelo* [25], the artist described the symptoms of his urolithiasis, along with complaints of a "cruel pain" affecting one foot. This constellation of findings has led to the diagnosis of gout, a hypothesis that has been questioned by others claiming that there is no confirmatory documentation that Michelangelo was having knee pain around that time, nor is there evidence that this figure in Raphael's fresco was truly Michelangelo [26]. Moreover, the lack of the classical signs of joint inflammation in the mentioned painting raises suspicion toward the inflammatory nature of Michelangelo's disease. Recently, a group of researchers analyzed the available portraits of Michelangelo, focusing on the disease that affected the artist's hands. They proposed that Michelangelo was afflicted by a degenerative condition of the joints, known today as osteoarthritis [27]. This diagnosis can be further supported by the fact that Michelangelo lost his dexterity only when he was relatively old. Indeed, he was seen sculpting up to 6 days before he died, at the age of 89 years. The authors concluded that by continuing hammering and painting, Michelangelo was able to maintain function in his hands for many years.

IT IS ALL IN YOUR BRAIN

Among the well-renowned masterpieces of Michelangelo is the *Creation of Adam*, a fresco painted on the ceiling of the Sistine Chapel in Rome [Figure 8]. It is considered one of the best known works in the history of art and is located in the most visited chamber in the world. This painting demonstrates God and Adam reaching toward one another with fingers outstretched, whereby God is believed to be providing Adam with the gift of life. This depiction is thought to represent the *primum movens*–the creation of the human being. In fact, the competency of Michelangelo in human anatomical

Figure 7. *The School of Athens*, Raphael, 1509–1511, Apostolic Palace, Vatican City

Figure 8. *The Creation of Adam*, Michelangelo, 1508–1512, Sistine Chapel, Rome

dissection is reflected in the hidden details of the drawing. In recent years, several medical interpretations of this scene have been suggested [28,29]. The first theory, proposed by Meshberger [30] in 1990, suggests that God is depicted as embedded in the shape similar to that of a human brain. When examining the outer shell of the image that surrounds God and the angels, and comparing it to the anatomical drawing of the skull by Frank Netter [30], a clear resemblance is revealed. Minute neuroanatomic structures can be identified, such as the pons, represented by the back of the angel extending laterally below God, and the pituitary stalk and gland depicted by the leg and foot of the angel that extends below the base of the picture. Meshberger concluded that when in the larger image, the fresco of Michelangelo delivers the message of the intellect as the gift of God to Adam. Apart from this common "Brain–God" theory, other interpretations have been raised, such as the similarity of the shape painted behind the figure of God with that of kidneys, which corresponds with the history of Michelangelo's renal stones. A group of Italian scientists has raised an alternative plausible explanation for this remarkable painting–a unique obstetric-themed context [31]. They posit that since Michelangelo had been commissioned to paint an ideal birth, the shape encompassing God is analogous to a uterus, with the choir of angels resembling the placenta. Whatever the interpretation, the *Creation of Adam* allows us, as physicians, to pursue further clues and symbols in artworks and paintings, developing our observation techniques and thus improving our clinical skills.

PHOTOSENSITIVITY SINCE THE 18TH CENTURY

The Parasol, also known as *El Quitasol* [Figure 9], is one of the most famous paintings by Francisco Goya. Although not yet described in terms of medical interpretation, we note a particular relevance of this painting to systemic lupus erythematosus (SLE).

In this work, Goya painted a woman sitting on the ground, holding a fan in her right hand. A young man is holding the parasol to shade the woman's face. Sharp-eyed viewers will notice the malar-like rash on the cheekbones of the young woman. The way the man is standing, with one foot on the rock and the other on the ground, suggests he is shading the woman from the harmful rays of the sun, which are known to exacerbate the skin rash typical of SLE.

Figure 9. *The Parasol*, Francisco Goya, 1777, Museo Nacional Del Prado, Madrid, Spain

SUMMARY

The observation of artwork, studying each line, color, and particular details that make the work intricate in itself not only gives one a firmer grasp and greater appreciation of the art, but can also enhance examination skills.

"Art," Southgate wrote in 2011, "whether it manifests as paintings, sculptures, poems, symphonies, or the care of patients, is a uniquely human quality. It signifies the unquenchable human quality of hope. … It acknowledges the human need to communicate, to share both the knowledge and the art of living well, to confront together the uniquely human enigma of pain, suffering, and death. … Painters and physicians know this well. Observation is not merely data collection such as any computer can record. It is not merely looking, it is seeing. It is not only listening, it is hearing. Its task is to enable the artist to complete what nature has not." [32,33]

CONCLUSIONS

In conclusion, understanding a complex medical problem requires the physician to search for clues beyond science, which may shed light on the correct diagnosis, demonstrating the integration of medical science with art and the humanities [34,35].

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Capsule

Foiling bad bugs' sneaky tricks

Intestinal pathogens can invade host cells and disrupt critical cellular functions, including secretion. Secretion is necessary for the delivery of antimicrobial proteins that kill pathogenic bacteria. **Bel** and co-authors showed that when intestinal epithelial cells sense an invading bacterial pathogen, they "reroute" the antimicrobial protein lysozyme through an alternative autophagy-based secretion pathway. This ensures lysozyme delivery to the gut lumen, which protects against further bacterial invasion. Secretory autophagy was triggered by endoplasmic reticulum stress and required signals from type 3 innate lymphoid cells. Thus, the innate immune response to gut pathogens co-opts autophagy in intestinal immune defense.

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Eitan Israeli

Capsule

KLF4-dependent perivascular cell plasticity mediates pre-metastatic niche formation and metastasis

A deeper understanding of the metastatic process is required for the development of new therapies that improve patient survival. Metastatic tumor cell growth and survival in distant organs is facilitated by the formation of a pre-metastatic niche that is composed of hematopoietic cells, stromal cells, and extracellular matrix (ECM). Perivascular cells, including vascular smooth muscle cells (vSMCs) and pericytes, are involved in new vessel formation and in promoting stem cell maintenance and proliferation. Given the well-described plasticity of perivascular cells, **Murgai** and co-authors hypothesized that perivascular cells similarly regulate tumor cell fate at metastatic sites. The authors used perivascular-cell-specific and pericyte-specific lineage-tracing models to trace the fate of perivascular cells in the pre-metastatic and metastatic microenvironments. They showed that perivascular cells lose the expression of traditional vSMC and pericyte markers in response to tumor-secreted factors and exhibit increased proliferation, migration and ECM synthesis. Increased expression of the pluripotency gene *Klf4* in these phenotypically switched perivascular cells promoted a less differentiated state, characterized by enhanced ECM production, that established a pro-metastatic fibronectin-rich environment. Genetic inactivation of *Klf4* in perivascular cells decreased formation of a pre-metastatic niche and metastasis. These data revealed a previously unidentified role for perivascular cells in pre-metastatic niche formation and uncovered novel strategies for limiting metastasis.

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