Cancer in a young child is unusual and has always aroused curiosity. Proptosis and an enormous, rapidly growing unilateral tumor in a 3-year-old boy prompted Pieter Pauw (1564-1617), a 16th-century anatomist, to perform an autopsy. His published notes from the autopsy were rediscovered in the 19th century, first by the German ophthalmologist and historian Julius Hirschberg and then by Edwin B. Dunphy, from Boston, Mass, who suggested that the child suffered from retinoblastoma, an interpretation that has held sway. Critical translation of the original Latin text suggests that an orbital tumor, such as embryonal rhabdomyosarcoma, would equally well explain Pauw's observations. His description also gives insight into the concept of a mole as a congenital as well as an intrauterine tumor in Renaissance medicine.
feat of the Spanish Armada, Pauw got a position as the professor of anatomy and botany in the Academy of Leiden, which he held until his death in 1617 at age 53 years (Figure 1). Many of Pauw’s early dissections were postmortems, from which he kept notes. In 1597, the very year when the eye tumor was dissected, he completed the first anatomical theater in Northern Europe and soon won the right to dissect executed criminals. His published autopsy notes then dwindle and eventually cease in 1602.

Dunphy had Pauw’s autopsy report translated from Latin for his talk and quoted it “in its entirety.” He made the qualification that the tumor Pauw encountered “of course may have been something else,” but he felt that “there is just enough similarity to what we know as retinoblastoma to feel that this may be the first case ever reported.” Authors who subsequently have cited Dunphy’s presentation have been less reserved. Even Sir Stewart Duke-Elder in his System of Ophthalmology, published 4 years later in 1967, accepted Pauw’s observation as an “unpublished” case of retinoblastoma. Many of Pauw’s early dissections were postmortem, from which he kept notes. In 1597, the very year when the eye tumor was dissected, he completed the first anatomical theater in Northern Europe and soon won the right to dissect executed criminals. His published autopsy notes then dwindle and eventually cease in 1602.

Dunphy mentioned that he did not succeed in locating Pauw’s original article. In fact, none existed. The handwritten notes that Pauw kept were donated around 1637 by his son to Thomas Bartholin (1616-1680), a Danish anatomist, who edited and added 34 of Pauw’s observations to his own Historiarum Anatomicarum Rariorum, published in 1657. This credit is given in Bartholin’s introduction to the Observationes Anatomicae.

Two surgeons were present at the autopsy; the same surgeons also appear in observations VIII, XII and XVI. In Renaissance times, surgeons were members of the barber’s guild. Dutch surgeons had to attend a certain number of autopsies as a form of continuous medical education. A famous contemporary painting The Anatomy of Dr Nicholas Tulp by Rembrandt van Rijn (1606-1669) records such a teaching session in the neighboring merchant city of Amsterdam on January 31, 1632. It is less well known that Tulp was Pauw’s pupil.

The title word oculorum refers to the eyes in plural, but the fellow eye is not mentioned in the report, and it was thus most likely uninvolved. The plural form may indicate an attempt at generalization or an editorial error. Dunphy mentioned that he did not succeed in locating Pauw’s original article. In fact, none existed. The handwritten notes that Pauw kept were donated around 1637 by his son to Thomas Bartholin (1616-1680), a Danish anatomist, who edited and added 34 of Pauw’s observations to his own Historiarum Anatomicarum Rariorum, published in 1657. This credit is given in Bartholin’s introduction to the Observationes Anatomicae.

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pugnus to describe sizes of other lesions as well, suggesting that it may have been the adult fist. If so, the tumor really was of unusual size.

This sentence is the first key to evaluating whether Pauw was dealing with a retinoblastoma. Dunphy translated it as “tumor of the left eye.”1 Taken literally, however, the phrase tumor ex oculo sinistro translates to “a tumor coming out of the left eye.” We believe that with oculus, the eye, Pauw is here referring to the orbital contents as a whole. This is evident when he next focuses to the eyeball by using the words bulbus oculi or.

Significantly, Pauw describes the eyeball using the adjective integer, which translates to something that is whole, intact, untouched, or pure. Dunphy choose the word “whole” for his translation.1 However, whole would be closer to the Latin totus, which would have been a natural choice if Pauw meant to say that the entire eye was pushed forward. Integer is derived from the Latin word tangere, to touch, and, thus, the most literal English translation would be “untouched.” Another possibility is “intact,” which directly derives from the Latin tangere. Pauw seems to indicate that the eyeball itself had been unharmed by the tumor.2

According to Pauw’s description, not only the eye but also its muscles apparently survived the tumor, at least initially. Retinoblastoma is an infiltrating cancer, and when it breaks through the sclera and optic nerve to the orbit, it typically destroys the eyeball. This can be readily confirmed from period drawings (Figure 2A) and, sadly, can sometimes be seen even today (Figure 2B and C). Before orbital extension occurs, the eye usually is filled with tumor (Figure 2D), and the pupil appears white in dim light, a sign that can be observed with the naked eye. Leukocoria is the most common initial symptom of retinoblastoma in regions such as Africa, India, and South America, where advanced disease is still frequent.1,14

Pauw next turns his attention to the temple, which had become affected by a second tumor 2 weeks previously; submandibular and preauricular lymph nodes would be a more typical site for metastatic retinoblastoma (Figure 2A and E). The tumor Pauw describes was located under a membrane, which Dunphy skipped in his translation.1 The words intra cutem, cranium; haerere are not easy to translate. The verb haere, which means to adhere to, to hang from, or to stick to something, would require an ablative or dative to identify the object. If Pauw used the comma to separate “skin” from this verb to communicate that the tumor was “inside the skin, adhering to the skull,” one would expect him to write intra cutem, cranii; haerere. Alternatively, had Pauw omitted the comma and written intra cutem cranium; haerere, the sentence would easily translate to “adhering inside the skin and the skull.” Perhaps Bartholin introduced an error here.

A third possibility is that the comma is used to emphasize the perhaps unexpected conclusion that the tumor would also be found intracranially, because -que can be translated as “and so,” “and also,” or “and especially.” At this point, the skull had not yet been opened but, because he had found a small opening, Pauw may have realized that the tumor must also have been present within the skull. Our translation is based on this assumption.

The opening in the skull must have been conspicuously small, because foraminulum is the diminutive of foramen, an opening, and the adjective exiguus, meaning small, tight, or narrow, makes it smaller still. Natura possibly indicates Pauw’s belief that the tumor had taken this route by the laws of nature rather than by divine or evil intervention; one of his postmortems was requested because of suspected witchcraft, a claim that he could not substantiate.

Dunphy and Hirschberg both thought that the intracranial part of the tumor was located between the bone and the dura mater.1,8 It may have been intradural, however, because Pauw wrote intra rather than inter in his description.2 He uses intra appropriately in several other reports from the same collection. However, the word inter never appears, and we must give Dunphy and Hirschberg the benefit of the doubt. Whatever the location, the intracranial tumor had not invaded the brain, which was undamaged like the eyeball.

In the same sentence, we reencounter the expression ocularis tumor, “tumor of the eye.” Again, Pauw appears to refer to an orbital rather than an intraocular tumor. It is clear that he opened the skull, but if he sectioned the eyeball, it is not mentioned in the report. The globe may have been destroyed by this time; Pauw does not tell us. He did section both tumors—the intracranial and the orbital—and found them to be of similar composition.

This last sentence is the second key point in the report, and, again, one that cannot easily be translated. The 2 components, brainlike tissue and clotted blood, are clearly stated, but what did mola refer to? Dunphy translated it as “like crushed stone,”17 which was likely inspired by the fact that a widely known meaning of mola is millstone. However, grains rather than stone are ground in mills, and it takes imagination to turn a millstone into gravel. Dunphy did not emphasize this part of the report,1 perhaps because he was not sure of his translation, but subsequent authors capitulated on it and suggested that Pauw recorded intratumoral calcifications, which are very typical of retinoblastoma.

In classical Latin, mola also had another meaning. It referred to a mixture of coarsely ground flour and salt, or mola salsa. Such a mixture was used especially to sprinkle offerings given to the gods in Hellenistic Greece. Even though calcifications of retinoblastoma might have resembled grains of salt, we consider this explanation to be unlikely, because mola salsa was not used in Medieval times, let alone during the Renaissance.

A third possible meaning is a mole or mooncalf, an abnormal mass formed in the womb, particularly one that contains fetal tissues. Today the definition has narrowed to mean especially complete and incomplete hydatidiform moles and invasive moles, pathologic conceptuses that result from genetically determined trophoblastic hyperplasia.15 This type of mole was first recorded in the literature by Aetius of Amida (527-565 AD) in Byzantium.16 Earlier in antiquity, the Roman naturalist Pliny the El-
der (23-79 AD) defined *mola* as a non-specific intrauterine mass when he wrote about human physiology in the seventh book of *Naturalis Historia*:

Solum autem animal menstruale mulier est; inde unius utero quas appellaverunt mo- las. Ea est caro informis, inanima, ferri ic- tum et aciem respuens; movetur sistitque et menses, ut partus, alias letalis, alias una se- nescens aliquando alvo citatore excidens.

Woman is, however, the only animal that has monthly periods; consequently she alone has what are called moles in her womb. This mole is a shapeless and inanimate mass of flesh that resists the point and the edge of a knife; it moves about, and it checks menstruation, as it also checks births: in some cases causing death, in others growing old with the patient, sometimes when the bowels are violently moved being ejected.

Pliny’s books were based mainly on extensive knowledge of literary sources rather than personal observation. It is possible that Pliny had not seen a mole himself. This might affect the accuracy of his description, but the fact remains that Pliny appears to use *mola* as an established technical term to describe intrauterine tumors, and his work was held in esteem throughout the Middle Ages. Eventually Nicolo´ Leoniceno (1428-1524), an Italian Hellenist, started to criticize the lack of accuracy in *Naturalis Historia*, and others followed suit. By the time Pauw studied medicine, Pliny’s influence had waned.

Figure 2. Advanced orbital malignancies in young children. A, Advanced retinoblastoma (Nancy Chisholm, Case 1. In: Wardrop J. *Observations on Fungus Haematodes or Soft Cancer*. Edinburgh, Scotland: George Ramsay & Co; 1809). Reprinted from the Royal College of Surgeons of Edinburgh. B and C, Advancing stages of extraocular retinoblastoma in the orbit and progressive destruction of the globe (courtesy of Santosh Honavar, MD, LV Prasad Eye Institute, Hyderabad, India). D, Leukocoria in one eye with extraocular retinoblastoma and a destroyed globe in the other orbit (courtesy of Paula Summanen, MD, Khartoum Eye Hospital, Khartoum, Sudan). E, Regional metastasis from retinoblastoma to submandibular and preauricular lymph nodes (courtesy of Jarmo Kuronen, MD, Haydom Lutheran Hospital, Tanzania). F, Advanced rhabdomyosarcoma of the orbit (courtesy of Dr Summanen).
Mola as an intrauterine tumor was nevertheless well known to Pauw because it appears in 2 of his autopsy reports. “Observatio XIX,” recorded in 1601, describes an intrauterine mola, white and consisting of scarred nodes, and “Observatio XXXI,” recorded a year later, describes a mola that had transformed into a honey-like substance that flowed out when the womb was opened.

What, then, was molae substantia in Pauw’s nomenclature? The solution is suggested by “Observatio XVII,” a fourth report in which mola appears. The autopsy, “Anatomy of a Monster,” was conducted in 1596, and it describes a newborn baby who died of mola occipiti soon after birth.28 This mola was the size of the child’s head and was covered by skin, dura, and pia mater; it emerged from an opening in the occipital bone and contained blood and clotted blood, a description suggestive of an occipital encephalocele. Pauw probably choose to call it a mole because it resembled his understanding of this medical term and because the tumor had unquestionably arisen in the womb.

We believe that the orbital and intracranial mass, which also consisted of clotted blood and tissue resembling brain, reminded Pauw of the fleshy masses, such as the mola occipiti he had seen just a year earlier, that were known as moles to physicians of his time; therefore, he choose the expression molae substantia for this tumor in a young child. He is careful not to state that the tumor was a true mole, presumably because it arose in childhood and not in the womb, but it substantially resembled one. Substantia, as compared to materia, means something that is particular, characteristic, or substantial to the nature of what is being described. Julius Hirschberg’s rendering, wie Hirnmark, mit geronnenem Blut, nicht anders als wie eine Mole—“like brain, with coagulated blood, not unlike a mole”—is right,8 but Hirschberg did not say how he defined the term mole. Blodi’s translation, “not unlike a dead, degenerating fetus,” appears too specific, considering that in those days a mole could also mean other intraterine and, apparently, congenital masses. What emerges from Pauw’s careful observation is a description of a rapidly growing orbital tumor, which caused problems initially by mass effect rather than infiltration. It did not destroy the eye, the extracranial muscles, and the brain, but it probably extended from the orbit into the intracranial space or vice versa; an actual connection between the orbit and intracranial space is not mentioned. We find no reference to an intracranial tumor and calcifications.

Such a history would be typical of a combined congenital orbital and intracranial teratoma, which is a rapidly growing but non-infiltrating developmental tumor.19 The classic description is that of an intact eye being pushed out of the orbit on top of a monstrous mass, which the extraocular muscles sculpt into a quadrangular shape. The intracranial portion pushes the brain, and extracranial extension is not uncommon, possibly because of associated bony defect. However, such a congenital tumor would not be expected to arise in a 3-year-old child.10

The most common rapidly growing orbital malignancies in this age group, and, thus, prime candidates to account for Pauw’s observation, are embryonal rhabdomyosarcoma and metastatic neuroblastoma,20,21 although their frequency may have changed over time. Of rhabdomyosarcomas, two thirds are diagnosed during the first decade, often in children younger than 3 years.22 The typical manifestation is acute exophthalmus. The eye is pushed forward and compressed, but it is initially otherwise unharmed. The gross appearance typically is a whitish fibrous mass with loose myxoid stroma.21 Rhabdomyosarcoma can extend into the intracranial cavity, and intratumoral hemorrhage is a recognized feature.23 These tumors can grow into huge masses that are larger than 2 fists (Figure 2F).22

The mean age at diagnosis of metastatic neuroblastoma is 2 years, and 1 in 12 children has orbital metastasis as the initial sign.21 Neuroblastoma is known for its propensity to undergo necrosis and hemorrhage, and it would resemble brain tissue by gross pathologic analysis. Neuroblastoma frequently involves adjacent bone. It might be argued, however, that Pauw should then have spotted an abdominal tumor as well and that metastases would very likely have been found in the brain, which would thus not have appeared unharmed.21

Other rapidly growing orbital malignancies in children include leukemia and metastases from Ewing sarcoma, medulloblastoma, and Wilms tumor.20,21 Even benign tumors, such as lymphangioma and neurofibroma, can sometimes cause huge orbital masses, but they would not be likely explanations in this context.20,21 The list is almost endless, because essentially any tumor occurring in the human body can also arise in the orbit. Pauw does not give us enough information to favor any alternative over the others.2

Retinoblastoma may have existed as long as humankind. Just how long ago this fascinating tumor first appeared in the literature is likely to remain a matter of debate. The purpose of our treatise has not been to discredit Pauw’s observation as a possible first description of retinoblastoma, which it may have been; after all, age 3 years would be typical for manifestation of unilateral, nonhereditary retinoblastoma, and the clinical signs do not exclude this diagnosis. Instead, we have attempted to point out features in Pauw’s report which open avenues for alternative explanations.

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