Published in final edited form as:

J Neuroophthalmol. 2020 September ; 40(Suppl 1): S7–S14. doi:10.1097/WNO.0000000000000988.

Wilbrand's Knee: To Be or Not to Be a Knee?

Jonathan C. Horton, MD, PhD

Department of Ophthalmology, Program in Neuroscience, University of California San Francisco, San Francisco, California

Abstract

Wilbrand's knee of the optic chiasm refers to crossing fibers from one optic nerve that stray for a short distance into the opposite optic nerve before joining the optic tract. This loop of aberrant axons, although small, has generated much controversy. In a previous study, labeling of the optic pathway in normal monkeys with a radioactive tracer revealed no Wilbrand's knee. Monocular enucleation induced a typical knee to form. These findings suggested that Wilbrand's knee is absent normally, but appears after atrophy of one optic nerve. This conclusion has been challenged by images showing Wilbrand's knee in the normal human chiasm using anisotropic light scattering. It has also been resisted by some clinicians who believe that Wilbrand's knee is necessary to explain the anterior chiasmal syndrome. Early in his distinguished career, William F. Hoyt examined the fiber organization of the monkey optic nerve and chiasm. He found no evidence for Wilbrand's knee and rejected its importance for the topical diagnosis of chiasmal lesions. His conclusion is supported by new data showing that anisotropic light scattering is not a reliable method for tracing axons. Hence, that method has given a misleading impression that Wilbrand's knee exists in normal subjects. Although Wilbrand's knee has fascinated neuro-ophthalmologists for more than a century, it is an inconsequential structure that develops only after a longstanding monocular optic neuropathy.

In the summer of 1978, I persuaded David Hubei to let me work in his laboratory. To get started, I needed a project. He suggested I look at the arrangement of retinal ganglion cell axons in the optic nerve. Years earlier, he had recorded from the monkey optic nerve with Torsten Wiesel. They had noticed that receptive fields were encountered almost randomly when a microelectrode advanced through the nerve (1). Hubei was perplexed when subsequently Hoyt and Luis published diagrams of parallel axons coursing through the monkey optic nerve and chiasm in nearly perfect retinotopic order (2,3). The discrepancy had snagged in his mind, and he thought it was worth resolving.

The issue was of scientific interest for the light it might shed on the mystery of how ganglion cell axon terminals during development find their targets in the precisely organized retinotopic map of the lateral geniculate nucleus. One theory was that the fibers retain their relative spatial relationships as they grow through the optic nerve, enabling them to synapse

Address correspondence to Jonathan C. Horton, MD, PhD, William F. Hoyt Professor of Neuro-Ophthalmology, Department of Ophthalmology, University of California, San Francisco, Beckman Vision Center, 10 Koret Way, San Francisco, CA 94143-0730; hortonj@vision.ucsf.edu.

The author reports no conflicts of interest.

with the appropriate geniculate neuron much like the pins in a computer cable might plug into a device (4). If fibers were jumbled in the optic pathway, that idea would be gutted.

SCATTERED AXONS IN THE OPTIC NERVE

Recording from the optic nerve was like kicking a beehive. The units were all over the place, and they buzzed away furiously. I remember scrambling to map my first receptive field and finding it on the ceiling of Hubei's laboratory. Next, we made tiny injections of a retrograde tracer into the lateral geniculate nucleus. Coronal sections were cut from the injection site to the optic nerve head. It was possible to follow individual axons section-by-section back to their cell bodies in the retina. The anatomy complemented the physiology beautifully: fibers were well organized at the optic disc but dispersed as they began coursing toward the optic chiasm. When they reached the lateral geniculate nucleus, they regrouped to form a compact bundle. We rushed off a short article describing nonretinotopic order in the optic nerve, although we allowed that "some crude topography may be preserved" (5). Regrettably, I never wrote up a full account of these experiments because I was so eager to get started exploring the visual cortex. Later, Jumpei Naito published a series of elegant articles confirming our findings (6,7). He noted that "It has been claimed that there is a distinct retinotopy in the monkey chiasm, despite lack of any clear anatomical evidence. However, the present data indicate a rather gross retinotopy or almost no discernible retinotopy."

NO WILBRAND'S KNEE IN NORMAL MONKEYS

A decade later, I was looking for a neuro-ophthalmology fellowship. At Simmons Lessell's suggestion, I wrote a letter of inquiry to Bill Hoyt. I decided it would be best not to mention my previous work on the optic nerve. That bit of diplomacy was wasted (Fig. 1), but Hoyt bore no grudge, and to my delight was willing to have me as a fellow. Afterward, I ended up joining the UCSF faculty and opening my own research laboratory. My first projects focused on the ocular dominance columns in the primary visual cortex of various species of monkeys. The columns were labeled, using a technique pioneered by Grafstein and Laureno, by injecting [^3H] proline into the vitreous of one eye (8). The tracer was transported along the optic nerve to the lateral geniculate nucleus and then transneuronally to layer 4C of striate cortex (9–11).

It occurred to me that as a side project, it should be easy to investigate Wilbrand's knee by cutting sections through the optic chiasm. Wilbrand famously had reported that decussating optic nerve fibers detour into the contralateral optic nerve before entering the optic tract (12). This aberrant loop of fibers came to be known as "Wilbrand's knee." He postulated that a lesion just anterior to the optic chiasm would produce vision loss in one eye and a superior temporal field cut in the other eye, owing to compression of the knee (13). When tracing labeled axons in Hubel's laboratory I had never noticed any deviating into the wrong optic nerve, so I was suspicious.

A horizontal section through a macaque optic chiasm after [^3H]proline injection into one eye is shown in Figure 2. Labeled and unlabeled fibers interleave in the chiasm, but no labeled fibers enter the opposite optic nerve. Not only is Wilbrand's knee absent, but fibers from

the labeled nerve actually avoid the entry zone of the other optic nerve. To confirm this finding, the optic pathway was sectioned coronally in other monkeys, and autoradiographs were prepared of the optic nerves just anterior to the chiasm and at the point where they join together (Fig. 3). No fibers from the labeled optic nerve were present in the unlabeled optic nerve. Only after the nerves become conjoined do fibers begin to stream across the optic chiasm. In 8 macaques and 3 squirrel monkeys, no evidence of Wilbrand's knee could be found (14).

WILBRAND'S KNEE INDUCED BY MONOCULAR ENUCLEATION

Wilbrand documented his knee in 2 patients, both blind in one eye. Atrophy of axons from the blind eye made it possible for him to show the path followed through the chiasm by axons from the healthy eye using classical neuroanatomical fiber and myelin stains. It was impossible for him to address whether the knee exists in normal subjects because, if both eyes are intact, the chiasm seems uniform when stained with such techniques. Polyak later drew diagrams showing the knee in normal humans, but they are simply schematic illustrations based on Wilbrand's work (15).

I hypothesized that Wilbrand's knee does not exist in normal subjects but is induced by monocular blindness. To test this idea, I enucleated one eye of a macaque monkey and waited 4 years. Then, I injected the remaining eye with [^3H] proline. The nerve corresponding to the missing eye was severely atrophic. The chiasm showed a knee of healthy fibers in the atrophic proximal nerve, just as shown by Wilbrand. The knee was labeled by myelin stains and autoradiography (Fig. 4). I proposed that shrinkage of the chiasm, caused by atrophy of one eye's axons, shortens the path length of healthy, decussating fibers. The slack fibers seem to herniate into the stump of the dead nerve. Thus, Wilbrand's knee is an artifact of monocular blindness. It is not present in normal humans or in patients with bitemporal hemianopia from a chiasmal tumor.

HOYT AND THE MISSING KNEE

When I told Bill Hoyt about my findings, he gripped my arm, leaned into me, and said in a lowered tone, "I didn't find one either." He went to a cabinet, pulled out a laboratory notebook, and sat me down at his oak table to show me drawings of experiments performed 30 years previously. He had made lesions in the retina of 30 macaques with a xenon arc lamp photocoagulator and then traced degenerating fibers through serial sections using the Nauta method. On his drawing of the nerves just before the chiasm, he had written boldly "No knee" (Fig. 5) and concluded with the notation "No knee formation at all." He made me copies of the original 35-mm slides capturing the histological slides drawn in Figure 5.

The Nauta method was notoriously fickle. Sometimes, it failed to label degenerating fibers, and sometimes, normal fibers seemed to be degenerating. Hoyt told me that he had not been sure what to make of his findings. In the article, he wrote that looping fibers "did occur in some of our animals; this seemed to be related to the angle at which the two optic nerves joined at the chiasm. When the anterior chiasmal notch was rounded or wide, no crossing axons detoured in the optic nerve" (3). His doubt was reflected in his instructions to Joan

Esperson, the talented medical illustrator who later created many of the figures for “The Book” (16). In a preceding article (2), she had drawn Wilbrand’s knee, but now, Hoyt told her to leave it out (3).

IMAGING THE UNLABELED OPTIC CHIASM

In 2014, Shin and colleagues (17) reported evidence for Wilbrand’s knee in the normal human optic chiasm. This finding garnered considerable attention because never before had the knee been shown in normal human autopsy specimens. They photographed axial 25- μ m-unstained sections by orienting light at 3 incident angles to exploit the anisotropic reflecting properties of optic axons. After digital images were acquired, they were pseudocolored red, green, and blue and merged to reveal “an anomalously oriented fiber tract that reversed direction at the optic nerve-chiasm junction...consistent with Wilbrand and Saenger’s original description.” Intrigued by their findings, I retrieved my sections of optic chiasm from storage, where they had been safeguarded for 25 years. I soaked sections in xylene to remove the coverslips and then stripped away the radiosensitive emulsion and silver grains (18). This yielded axial 30- μ m-unstained, unlabeled sections, just like those examined by Shin and colleagues. I photographed them as he described. By orienting light at 3 different angles and merging pseudocolored images, I generated something that looks remarkably like Wilbrand’s knee (Fig. 6A). However, comparison with a picture of the same section (Fig. 6B) taken before removing the autoradiographic emulsion shows that radiolabeled fibers from the other optic nerve bear no relationship to the “Knee” created by digital manipulation of illumination, color, contrast, and brightness. In short, the knee imaged using this technique is a photographic artifact that does not represent Wilbrand’s knee.

WILBRAND’S KNEE: FUGGEDABOUTIT

The conclusion that Wilbrand’s knee is an artifact of monocular vision loss has been greeted with skepticism by a few colleagues. As an inveterate skeptic myself, I understand the high level of evidence required before discarding classical neuroanatomical concepts. I point out, however, that the existence of Wilbrand’s knee in normal subjects has never been supported by any reliable evidence—it was extrapolated from patients blind in one eye. Given that no knee exists in normal monkeys, but one is induced to form by monocular enucleation, it seems logical to conclude that the same holds true in humans.

Sadun and colleagues (19) have cut serial 4- μ m axial sections through a normal human chiasm and traced individual fibers labeled with the Bielschowsky and Bodian methods. They could not detect Wilbrand’s knee. Kosmorsky and colleagues (20) have observed that resection of an optic nerve just before the chiasm does not produce a superior temporal field defect in the other eye. It may help change some minds to know that Bill Hoyt looked in vain for Wilbrand’s knee and eventually decided that it does not exist. But as Asa Gray, the great American botanist wrote in 1860: “we cling to a long-accepted theory, just as we cling to an old suit of clothes.” Recently, while browsing textbooks for sale in the lobby outside a meeting hall, I discovered an illustration based on one of Hoyt’s diagrams of the optic chiasm (Fig. 18 in [3]). It had been corrupted to show a knee where Hoyt took pains to show none. One can only imagine Bill’s reaction to that textbook.

One reason that Wilbrand's knee persists in textbooks is that some physicians believe it is required to explain certain patterns of visual field loss, namely a junction scotoma from a prechiasmal lesion. They invoke the anterior chiasmal syndrome as evidence for Wilbrand's knee (21). In this syndrome, a lesion compresses one nerve right before the chiasm to produce an optic neuropathy. Sometimes, there is diffuse visual field loss (usually with a temporal flavor) and acuity reduction. In other cases, there is only a temporal field cut and normal acuity. In either instance, an early, superior wedge of temporal field loss is often present in the other eye. The defect in the other eye is believed to be due to Wilbrand's knee. In fact, when a visual field defect is present in both eyes, careful review of the neuroimaging will show that the lesion also compresses the optic chiasm. Even when a tumor seems to show pure optic nerve compression, on closer scrutiny, there is invariably some element of chiasmal compression (22,23). The visual field defect is the combined result of compression of ganglion cell axons in both the optic nerve and chiasm. Once this point is appreciated, it becomes easier to let go of Wilbrand's knee.

Contrary to popular belief, a junction scotoma does not reliably localize a sellar tumor to the prechiasmal region. We all have cherry-picked cases in our teaching files that seem to prove otherwise, for example, a small tuberculum sella meningioma compressing one optic nerve and the anterior chiasm. But often, one may encounter a tumor right underneath the chiasm, such as a pituitary adenoma, producing a perfect junction scotoma. It occurs because sellar tumors usually damage the optic chiasm in an asymmetrical fashion and involve the optic nerve(s) as well (Fig. 7) (24). Most textbooks depict a symmetrical bitemporal hemianopia from chiasmal compression, but that pattern of field loss is unusual enough that some authors have playfully called it a myth (25). Junction scotoma is quite common from routine tumors that compress the optic chiasm and not a feature unique to prechiasmal optic nerve compression.

It was by chance that Bill Hoyt and I, early in our careers, both shared an interest in the fiber organization of the primary optic pathway in monkeys. We recognized independently that Wilbrand's knee is a bit of trivial misinformation. After he completed his anatomical studies, Hoyt never returned to the laboratory bench. He became consumed by the task of writing *Clinical Neuro-Ophthalmology* with Frank Walsh. That book brought him fame, and a reputation as an unsurpassed scholar, clinician, and teacher. Although he was not a scientist, his interests remained keenly focused on the problem of correlating clinical findings with the anatomy and physiology of the visual system. Sharing the past 30 years at UCSF with him was among the greatest privileges of my career.

ACKNOWLEDGMENTS

The author thanks Dr. Robert Laurenco and Dr. Richard Sogg (Hoyt's first fellow, 1961–1962) for their review of the manuscript.

Supported by grants EY029703 (J.C.H.), EY02162 (Beckman Vision Center) from the National Eye Institute and by an unrestricted grant from Research to Prevent Blindness.

REFERENCES

1. Hubel DH, Wiesel TN. Receptive fields of optic nerve fibres in the spider monkey. *J Physiol.* 1960;154:572–580. [PubMed: 13716437]
2. Hoyt WF, Luis O. Visual fiber anatomy in the infrageniculate pathway of the primate. *Arch Ophthalmol.* 1962;68:124–136.
3. Hoyt WF, Luis O. The primate chiasm. Details of visual fiber organization studied by silver impregnation techniques. *Arch Ophthalmol.* 1963;70:69–85. [PubMed: 13955217]
4. Horder TJ, Martin KA. Morphogenetics as an alternative to chemospecificity in the formation of nerve connections. A review of literature, before 1978, concerning the control of growth of regenerating optic nerve fibres to specific locations in the optic tectum and a new interpretation based on contact guidance. *Symp Soc Exp Biol.* 1978;32:275–358. [PubMed: 382425]
5. Horton JC, Greenwood MM, Hubel DH. Non-retinotopic arrangement of fibres in cat optic nerve. *Nature* 1979;282:720–722. [PubMed: 514350]
6. Naito J Retinogeniculate projection fibers in the monkey optic nerve: a demonstration of the fiber pathways by retrograde axonal transport of WGA-HRP. *J Comp Neurol.* 1989;284:174–186. [PubMed: 2474002]
7. Naito J Retinogeniculate projection fibers in the monkey optic chiasm: a demonstration of the fiber arrangement by means of wheat germ agglutinin conjugated to horseradish peroxidase. *J Comp Neurol.* 1994;346:559–571. [PubMed: 7527062]
8. Grafstein B, Laureno R. Transport of radioactivity from eye to visual cortex in the mouse. *Exp Neurol.* 1973;39:44–57. [PubMed: 4121484]
9. Horton JC, Hocking DR. Anatomical demonstration of ocular dominance columns in striate cortex of the squirrel monkey. *J Neurosci.* 1996;16:5510–5522. [PubMed: 8757263]
10. Horton JC, Hocking DR. Timing of the critical period for plasticity of ocular dominance columns in macaque striate cortex. *J Neurosci.* 1997;17:3684–3709. [PubMed: 9133391]
11. Horton JC, Hocking DR. An adult-like pattern of ocular dominance columns in striate cortex of newborn monkeys prior to visual experience. *J Neurosci.* 1996;16:1791–1807. [PubMed: 8774447]
12. Wilbrand H, Saenger A. *Die Neurologie des Auges.* Vol. 3, part 1. Wiesbaden, Germany: J. Bergmann, 1904:98–120.
13. Wilbrand H, Saenger A. *Die Erkrankungen des Chiasmas.* In: *Die Neurologie des Auges.* Vol 6. Wiesbaden, Germany: J. Bergmann, 1915:15–17.
14. Horton JC. Wilbrand's Knee of the primate optic chiasm is an artefact of monocular enucleation. *Trans Am Ophthalmol Soc.* 1997;95:579–609. [PubMed: 9440188]
15. Polyak S *The Vertebrate Visual System.* In: Klüver H, ed. Chicago, IL: Univ of Chicago Press, 1957.
16. Walsh FB, Hoyt WF. *Clinical Neuro-Ophthalmology.* 3rd edition. Baltimore, MD: The Williams and Wilkins Co, 1969.
17. Shin RK, Qureshi RA, Harris NR, Bakar D, Li TP, Jafri MS, Tang CM. Wilbrand knee. *Neurology.* 2014;82:459–460. [PubMed: 24491972]
18. Bianchi N, Lima-de-Faria A, Jaworska H. A technique for removing silver grains and gelatin from tritium autoradiographs of human chromosomes. *Hereditas (Lund).* 1964;31:207–2011.
19. Kolostyak KP, Ross-Cisneros FN, Sadun AA. The search for Wilbrand's knee. *Invest Ophthalmol Vis Sci.* 2006;47:801.
20. Lee JH, Tobias S, Kwon JT, Sade B, Kosmorsky G. Wilbrand's knee: does it exist? *Surg Neurol.* 2006;66:11–17; discussion 17. [PubMed: 16793428]
21. Schiefer U, Isbert M, Mikolaschek E, Mildenerberger I, Krapp E, Schiller J, Thanos S, Hart W. Distribution of scotoma pattern related to chiasmal lesions with special reference to anterior junction syndrome. *Graefes Arch Clin Exp Ophthalmol.* 2004;242:468–477. [PubMed: 15069563]
22. Karanjia N, Jacobson DM. Compression of the prechiasmatic optic nerve produces a junctional scotoma. *Am J Ophthalmol.* 1999;128:256–258. [PubMed: 10458197]
23. Horton JC. Compression of the prechiasmatic optic nerve produces a junctional scotoma. *Am J Ophthalmol.* 2000;129:826–828. [PubMed: 10970241]

24. Trobe JD, Tao AH, Schuster JJ. Perichiasmal tumors: diagnostic and prognostic features. *Neurosurgery*. 1984;15:391–399. [PubMed: 6483154]
25. Lee IH, Miller NR, Zan E, Tavares F, Blitz AM, Sung H, Yousem DM, Boland MV. Visual defects in patients with pituitary adenomas: the myth of bitemporal hemianopsia. *Am J Roentgenol*. 2015;205:W512–W518. [PubMed: 26496573]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

BERKELEY • DAVIS • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO

SANTA BARBARA • SANTA CRUZ

DEPARTMENT OF NEUROLOGICAL SURGERY
NEURO-OPHTHALMOLOGY UNIT
876 MOFFITT HOSPITAL
(415) 476-1130

SAN FRANCISCO, CALIFORNIA 94143

January 6, 1988

Jonathan C. Horton, M.D., Ph.D.
Department of Ophthalmology
Georgetown University Medical Center
3800 Reservoir Rd., N.W.
Washington, D.C. 20007

Dear Dr. Horton:

I have known your name since your publication in Nature in 1979. I did not know that you were now a resident in ophthalmology. I would be delighted to have you for a clinical fellow in neuro-ophthalmology in 1989 if you can work out arrangements for your financial support.

Please phone me for answers to your questions on my fellowship program. I am very glad to learn that you plan to pursue a career in academic neuro-ophthalmology. With your experience you should be able to make some significant contributions.

Sincerely,

A handwritten signature in dark ink, appearing to read "W. F. Hoyt", with a long horizontal flourish extending to the right.

William F. Hoyt, M.D.
Professor
Neuro-ophthalmology

FIG. 1.

Letter from Bill Hoyt offering a fellowship position in neuro-ophthalmology.

FIG. 2.

No Wilbrand's knee in normal monkeys. **A.** Axial section of the optic nerves and chiasm stained for Nissl substance. **B.** Autoradiograph of an adjacent section prepared after tritiated proline injection into one eye. The labeled nerve is dark. In the chiasm, labeled and unlabeled fascicles form a basket weave. Contrary to Wilbrand's report, labeled fibers from the injected eye avoid going near the entry zone (between *arrows*) of the unlabeled optic nerve where it joins the optic chiasm.

FIG. 3.

No fibers from the contralateral eye are present until the optic nerves join at the chiasm. **A** and **D**. Matching coronal light-field and dark-field images of the nerves 180 μm before the optic chiasm. **B** and **E**. At the point where the nerves become conjoined, there are still no labeled fibers in the left, unlabeled optic nerve. **C** and **F**. A section 120 μm farther posterior, showing fibers streaming from the labeled right side of the optic chiasm into the left side.

FIG. 4.

Creation of Wilbrand's knee. **A.** Axial section stained for myelin using the Gallyas method shows the macaque optic chiasm 4 years after enucleation of the right eye. Wilbrand's knee is present in the proximal, atrophied right nerve. **B.** Adjacent autoradiograph reveals labeled left optic nerve, with its fibers forming Wilbrand's knee on the right side. The chiasm is only 5-mm wide, compared with 6.5 mm in a normal animal (Fig. 2).

FIG. 5.

Hoyt's 1962 laboratory notebook includes drawings of serial coronal sections of monkey optic nerves joining to form the optic chiasm. He writes in top left image "**NO KNEE**" and concludes at bottom right "No knee formation at all." Inset: 35-mm slide from Hoyt shows tissue drawn on the left side. He noted on the plastic mount, "NO knee fibers #1."

FIG. 6.

Anisotropic light scattering reveals a false Wilbrand's knee. **A.** Section in Figure 2B, after removal of radioactive emulsion and silver grains, shows merged pseudocolored images taken with light at 3 different angles. The arrow denotes a structure that could be mistaken for Wilbrand's knee. **B.** Same section shown in Figures 2B and 6A but viewed in darkfield before removal of radiolabel. White arrows (matching *black arrows* in Fig. 2B) denote entry zone of right optic nerve. There is no label from the left optic nerve extending anterior to the optic chiasm, proving that the structure marked in (**A**) does not correspond to Wilbrand's knee.

FIG. 7.

Junction scotoma from a pituitary adenoma combines compression of the optic nerves and chiasm. **A.** Classical teaching attributes the visual field abnormalities in this patient to a lesion compressing the left optic nerve anterior to the optic chiasm, with the field loss in the right eye due to Wilbrand's knee. **B.** In fact, the tumor compresses the optic chiasm and both optic nerves (*arrows*). Correlation between tumor anatomy and pattern of visual field loss is often surprisingly unpredictable. dB, decibel; MD, mean deviation.