From Lesions to Loci: New Cartographies of the Brain

A young mother recovering from optic neuritis which had temporarily stolen her sight sat across from me, her baby resting in her lap. Years ago, she would have left this visit with a clear diagnosis of multiple sclerosis and a familiar treatment plan. Today, her antibody tests tell a more complicated story: negative for aquaporin-4, equivocal for MOG, MRI features not quite typical. She lives in the borderlands between definitions, suspended between diagnoses. Each new antibody discovery, from AQP4 to MOG, reveals hidden patterns of disease while fraying old definitions. For the clinician, the picture grows clearer in detail but dimmer in meaning; each new pixel adds resolution without understanding. This uncertainty is not purely academic. A generation ago, my patient would have started interferon therapy without question, yet today that same treatment could harm a patient whose illness lies just beyond the boundaries of multiple sclerosis as we now define it. The science has advanced, but the assurance of protocols that once guided care has thinned. Knowledge accumulates faster than meaning, refining our vision even as it blurs our confidence in what we see. We clarify the map while obscuring the terrain.

From its inception, neurology has required an unusual tolerance for ambiguity. When Jean-Martin Charcot lectured at the Salpêtrière in the 1860s, he described '*sclérose en plaques'* by correlating symptoms with autopsy findings—rarely in the same patient. His students, including Babinski and Freud, learned a discipline built on inference rather than certainty. Diagnosis rested on patterns glimpsed through the fog of incomplete information: a tremor's cadence, a reflex's delay, a lesion revealed only after death. The neurologist's art was not merely localization but interpretation—an anatomy of the invisible.

That spirit endured through the twentieth century. The lesion diagrams of Wernicke, the cortical maps of Penfield, and the taxonomies of Jackson all depended on assembling fragments of evidence into a coherent whole. Each new technology promised to replace uncertainty with clarity. From EEG to CT to MRI, every advance was heralded as an end to speculation. Suddenly, we could see what had been invisible.

When Hans Berger recorded the first EEG, he imagined it as a window into thought itself and a means to objectify epilepsy diagnoses. Instead, clinicians discovered a more ambiguous truth: epileptiform discharges in the healthy, normal tracings in confirmed epilepsy, and waveforms that required discernment rather than simple observation. The EEG did not eliminate uncertainty; it merely shifted it to a higher frequency.

MRI offered similar revelations. The ability to visualize the living brain transformed diagnosis but also uncovered countless incidental findings—minuscule infarcts, benign lesions, unexplained hyperintensities—that raised more questions than they answered. Each leap in technology made the unseen visible while demanding new judgment about what those images meant. The more precisely we measured, the less confidently we could perceive.

Trainees in neurology today enter the field at another inflection point. Modern neurology now decodes two immense, intertwined systems: the neural code and the genetic code. The first is a language of electrical impulses and interconnected networks; the second, a vast sequence of nucleotides encoding the instructions for building those very networks. Both are newly accessible at breathtaking resolution. High-field MRI traces white-matter tracts down to microns, while next-generation sequencing and single-cell transcriptomics generate terabytes of data per patient—each pixel and base pair a potential clue, every dataset its own Rorschach. In the clinic, these tools have transformed the landscape of disease. Where once we saw single entities such as multiple sclerosis, epilepsy, or migraine, we now see spectra of molecularly-distinct disorders.

Across the field—in neurodevelopmental syndromes, epilepsy, movement disorders and myriad others—genomic data illuminate mechanisms once hidden and identify hundreds of implicated genes per disorder. The genome tempts us with the promise of total explanation, yet interpretation remains probabilistic: "likely-pathogenic," "possibly-pathogenic," "variant of uncertain significance." The neurologist becomes a translator between code and consequence, explaining probabilities to families who want answers, not likelihoods. Prior authorizations hinge on categories; trial criteria calcify around biomarkers; a single letter in a report can open doors—or close them.

Even the concept of idiopathic illustrates this evolution. Once it reflected humility: a recognition that not knowing was itself a kind of knowledge. The idiopathic generalized epilepsies, for example, described recurrent seizures with no structural cause but predictable response to valproate. The diagnosis was imprecise but useful—it provided language, prognosis, and treatment. Genomic testing splintered that umbrella into gene-defined syndromes—*SCN1A*, *GABRG2*, *STXBP1*—each molecularly precise. Yet for patients whose sequencing reveals only variants of uncertain significance, the label of idiopathic is vanishing and no new certainty has replaced it.

As biomarkers sharpen disease boundaries, the number of unclassifiable cases paradoxically grows. Patients once grouped under the MS umbrella are now recognized as having antibody-mediated disorders such as NMOSD or MOGAD, while others meet neither serologic nor radiologic criteria—falling between categories and outside trial frameworks. Idiopathic may be fading from our vocabulary, but not from our reality.

The challenge is no longer data scarcity, as Charcot faced defining '*sclérose en plaques*', but data excess. We can record every neuron's firing pattern in a mouse brain yet struggle to explain consciousness. We can sequence every gene in a child with epilepsy yet fail to say why a given variant causes seizures in one patient and not another. Machine learning extends our ability to recognize patterns but not to understand them. AI models detect correlations beyond human sight, yet interpretation—the act of turning pattern into meaning—remains a human art.

If history offers guidance, it is that progress in measurement must be matched by wisdom in interpretation. The story of neurology is not chiefly one of eliminating ambiguity, but of learning to live with it more intelligently. EEGs are no longer read in isolation but weighed against the patient's story and timing; MRI findings demand clinicoradiologic correlation before shaping a diagnosis. On a recent overnight consult, seemingly-epileptiform EEG tracings tempted us to start levetiracetam. However, the story—brief loss of consciousness in a hot subway, rapid recovery, no postictal confusion—better fit syncope than epilepsy, and the young patient left with an explanation, but without an unnecessary drug. Each generation of tools teaches the same lesson: precision without context is noise.

Additionally, ambiguous variant data create new ethical frontiers. How do we counsel patients whose genomic results predict neurodegenerative disease decades before symptoms, or whose variants suggest risk but not inevitability? Precision medicine offers foresight but not always foreknowledge. We risk burdening patients with probabilities they cannot act upon and questions we cannot yet answer. But ambiguity is not failure—it is a feature of progress, a reminder that discovery outpaces understanding. It asks for humility and the discipline to translate uncertainty into thoughtful care.

As technology reshapes the boundaries of understanding, it also redefines the neurologist's role. The modern clinician must be as fluent in insight as in investigation—an arbiter of probability and a bridge between computation and meaning. In this sense, the neurologist becomes a translator of codes: electrical, genetic, and digital.

Even as the field grows more data-driven, its enduring craft lies in clinical discernment, contextual reasoning, and narrative synthesis—the ability to turn signal into meaning. Whether correlating a reflex with a lesion or a variant with a phenotype, the neurologist's task is to make sense of incomplete information. The interpretive skills honed since the pre-imaging era are precisely those needed to navigate the genomic one.

Perhaps ambiguity is not the enemy of neurology but its oldest companion. From the hand-drawn lesion maps of Charcot to the algorithmic connectomes of today, our instruments have changed but our epistemology has not. We still chart the brain's contours at the edge of the known.

The young mother with optic neuritis eventually recovered her vision. Her antibodies remain negative, her MRI unchanged. Her illness carries no label. In another era, she would have been diagnosed with multiple sclerosis, and that "certainty" could have brought relief—but also the wrong treatment. Her uncertainty is itself a kind of truth. It spares her the false assurance of an older cartography and leaves space for the maps still being drawn. Ambiguity reminds us that progress depends not only on data but on discernment. Those entering neurology inherit the lineage of Charcot's art of interpretation, though their fog is digital. The unseen is no longer hidden within tissue but buried in data. Our task has shifted from tracing lesions in wax to deciphering probabilities from opaque predictive models. Our instruments see more than we can parse, and our algorithms predict more than we can prove. The neurologist of tomorrow must arbitrate between patterns—between what algorithms find and what patients feel—translating computation into care. The art of neurology endures not because the unknown has vanished, but because it never will. Each generation must learn anew to see through the haze.