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REVIEW

Three before their time: neuroscientists whose ideas were ignored by their contemporaries

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Abstract I discuss three examples of neuroscientists whose ideas were ignored by their contemporaries but were accepted as major insights decades or even centuries later. The first is Emanuel Swedenborg (1688–1772) whose ideas on the functions of the cerebral cortex were amazingly prescient. The second is Claude Bernard (1813–1878) whose maxim that the constancy of the internal environment is the condition for the free life was not understood for about 50 years when it came to dominate the development of modern physiology. The third is Joseph Altman (1925–) who overturned the traditional dogma that no new neurons are made in the adult mammalian brain and was vindicated several decades later.

Keywords Emanuel Swedenborg · Claude Bernard · Joseph Altman · Neurogenesis · Internal environment · Before their time

Introduction

Sometimes, some of a scientist's ideas are rejected by their contemporaries or, more commonly, simply ignored. Much more rarely, these ideas become accepted as major insights decades or even centuries later. This paper considers three very different such cases in neuroscience, one from each of the last three centuries. I will discuss the context in which each of them worked, what their initially ignored discoveries were, why they were ignored and how they were finally recognized.

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Emanuel Swedenborg

Emanuel Swedenborg (1688–1772) was a Swedish nobleman, polymath and mystic who conversed with God and Angels and made a number of substantial contributions to astronomy, geology, metallurgy, paleontology and physics (Jonsson 1971; Toksvig 1848; Tafel 1877; Swedenborg Society 1911). Theology was a major interest and soon after his death, his followers founded the Swedenborgian Church of the New Jerusalem that continues today as an active Protestant sect (Jonsson 1971). Among his unrealized schemes were ones for airplanes, submarines, and machine guns. (Do all visionaries dream of flying through the sky, swimming beneath the sea and efficiently wiping out their enemies, or do Leonardo and Swedenborg have something special in common?)

In the 1740s, inspired by studying Newton, Swedenborg began seeking mathematical and mechanical explanations of the origin and nature of the physical and biological universes. For example, he developed a theory of the origin of planets similar to the later (and apparently independent) ones of Kant and Laplace. He then turned to the problem of the nature of the soul and its relation to the body. This led him to seek the site of the soul in the body and thus to the study of the brain. As he put it:

> I have pursued this [brain] anatomy solely for the purpose of discovering the soul. If I shall have furnished anything of use to the anatomic or medical world it will be gratifying, but still more so if I shall have thrown any light upon the discovery of the soul (Swedenborg 1849).

The cerebral cortex in Swedenborg's time

From the revival of anatomical investigation by Andreas Vesalius of Padua in the sixteenth century until the middle of the nineteenth century, the cerebral cortex was usually considered of little interest (Gross 1998a). This is reflected in its very name, "cortex", Latin for "rind". Vesalius himself thought the function of the cortical convolutions was to allow the blood vessels to bring nutriment to the deeper parts of the brain (Vesalius 1543).

A similar view was taken by Thomas Bartholin (1660–1680), Professor of Anatomy in Copenhagen and discoverer of the lymphatic system. He suggested that the convolutions were "to make the cerebral vessels safe by guiding them through these tortuosities and so protect them against danger of rupture from violent movements" (Bartholin 1656).

Marcello Malpighi (1628–1694), Professor in Bologna, the founder of microscopic anatomy and discoverer of capillaries, was the first to microscopically examine the cortex. He saw it as made up of little glands or "globules" with attached fibers (see Fig. 1.11 in Gross 1998a):

> I have discovered in the brain of higher sanguinous animals that the cortex is formed from a mass of very minute glands. These are found in the cerebral gyri which are like tiny intestines and in which the white roots of the nerves terminate or, if you prefer, from which they originate…[the globules] are of an oval figure…[their] inner portion puts forth a white nervous fibre…the white medullary substance of the brain being in fact produced by the connection and fasciculation of many of these (Malpighi 1666).

Similar "globules" or "glandules" were also reported by Leeuwenhoek and other subsequent microscopists (Meyer 1971). Historians once thought these pioneers were actually observing cortical pyramidal cells (e.g. Nordenskiold 1928). However, at least in the case of Malpighi, artifacts are now considered a more likely possibility, since Malpighi reported that the globules were more prominent in boiled than fresh tissue. Furthermore, artifacts similar to Malpighi's globules have been produced by "experimental historians" using the methods and instruments described in detail by Malpighi (Clarke and Bearn 1968).

Malpighi's view of the brain as a glandular organ was commonly subscribed to in the seventeenth and eighteenth centuries. Perhaps a reason for its popularity was that it fit with the still persisting views of Aristotle that the brain was a cooling organ and of the Hippocratic doctors that the brain was the source of phlegm (Gross 1995, 1998a). The only major figure to attribute any importance to the cerebral cortex was Thomas Willis (1621–1675), Professor of Natural Philosophy at Oxford and author of the first monograph on brain anatomy and physiology (Willis 1664). Although Willis denied both sensory and motor function to the cerebral cortex, he did attribute to it such higher functions as imagination and memory. However, even this interest in the cerebral cortex dissipated by the end of the century.

In the middle of the eighteenth century, physiology was dominated by Albrecht von Haller, Professor at Tübingen and later Bern. Using animals, he tested the "sensibility" of various brain structures with mechanical stimuli such as picking with a scalpel, puncturing with a needle and pinching with forceps as well as with chemical stimuli such as silver nitrate, sulfuric acid and alcohol. With these methods he found the cortex completely insensitive. By contrast, he reported the white matter and subcortical structures such as the thalamus and medulla to be highly sensitive; their stimulation, he said, produced expressions of pain, attempts of the animal to escape or convulsions (Neuburger 1897).

Throughout this period there was an emphasis on the structures surrounding the ventricles rather than the cerebral cortex. This was a tradition derived from the medieval doctrine of ventricular localization of psychological function (Gross 1993, 1998a).

Usually, the cerebral cortex was considered an insensitive rind with no sensory, motor or higher functions.

Swedenborg's writings on the brain

Swedenborg first published on the brain in 1740 in his *Oeconomia Regni Animalis*, which was later translated from Latin into English as *The Economy of the Animal Kingdom* (Swedenborg 1845–1846). By "regni animali" he meant kingdom of the animal or soul; he considered this kingdom to be the human body and, particularly, the brain. By "oeconomia" he meant organization. Thus a better translation of his title might be "Organization of the body" or less literally, "The biological bases of the soul." He also dealt with the brain and sense organs in his second major biological work *Regnum Animale* (Swedenborg 1843–1844) published in Latin in 1744.

In 1743, Swedenborg's religious visions began and for the rest of his life he concentrated his energies on religion and spiritual matters. He never returned to his former interest in the brain and indeed, much of his writing on the brain remained unpublished in his lifetime. In the nineteenth century a number of Swedenborg's manuscripts on the brain and sense organs were found in the library of the Swedish Academy of Sciences (Tafel 1877) and published, sometimes first in Latin and then in English. The most important of these was *The Brain* published in 1882 and 1887 (Swedenborg 1982, 1987). Further translations of Swedenborg's unpublished writings on the brain appeared in the twentieth century but these were mostly earlier drafts of material already published (e.g. Swedenborg 1914, 1922, 1938, 1940).

On the cerebral cortex

At the very beginning of his biological works Swedenborg announces that his writings will be based primarily on the work of others:

> Here and there I have taken the liberty to throw in the results of my experience, but only sparingly…I deemed it best to make use of the facts supplied by others…I laid aside my instruments, and restraining my desire for making observations, determined to rely rather on the researches of others than to trust my own (Swedenborg 1845–1846).

In fact, he very rarely does "throw in" the results of his own work. There is only a single figure of his own brain dissections, that of a drake (Swedenborg 1845–1846), and almost no accounts of any of his own experiments or observations.

Swedenborg began each part of his biological works with an extensive set of long quotations from previous writings on the subject. Then in the section following, entitled "Analysis" or "Induction," he proceeds to weave his own theory of biological structure and function. Such a section from *The Economy of the Animal Kingdom* (Swedenborg 1845–1846) on "The cortical substance of the brain" characteristically begins "From the forgoing experience we infer, that the cortex is the principal substance of the brain." In fact, his "inference" was actually a radical and total departure from the contemporary literature he had just reviewed. Swedenborg then goes on to argue that the cerebral cortex is the most important substance in the brain for sensation, movement and cognition:

> From the anatomy of the brain it follows that the brain is a sensorium commune with respect to its cortical substance…since to it are referred the impressions of the external sense organs as if to their one and only internal centre…The cortical substance is also the motorium commune voluntarium for whatever actions are mediated by the nerves and muscles are determined beforehand by the will, that is, by the cortex (Swedenborg 1845–1846).

> This must be taken as a general principle, that the cortical substance…imparts life, that is sensation, perception, understanding and will; and it imparts motion, that is the power of acting in agreement with will and with nature…(Swedenborg 1845–1846).

Central to Swedenborg's brain theory were the cortical globules or glandules described by Malpighi and his successors. In an extraordinary anticipation of the Neuron Doctrine, Swedenborg argued that these globules or, as he sometimes called them cerebella ("little brains"), were functionally independent units which were connected to each other by way of thread-like fibers. These fibers also ran through the white matter and medulla down to the spinal cord and then by way of the peripheral nerves to various parts of the body. The operations of these cerebella, he argued, were the basis of sensation, mentation and movement.

Sensory and motor functions of the cortex

Whereas Descartes (1972) had projected sensory messages to the walls of the ventricle and Willis (1664) had brought them to the thalamus, Swedenborg thought they terminated in the cerebral cortex, "the seat wherein sensation finally ceases," specifically in the cortical cerebella:

Swedenborg even outlines the pathway from each sense organ to the cortex, a totally unprecedented view and one that was not to reappear until well into the nineteenth century:

> …the visual rays flow, by means of the optic nerve, into the thalami nervorum opticorum, and are thence diffused in all directions over the cortex…Also the subtle touches of the olfactory membrane lining the labyrinthine cavities of the nares and the consequent subtle transformation or modifications…do not terminate until they arrive…in the cortical circumstance. Again the modulations of air, striking upon the delicate…internal ear allow themselves to be carried to the medulla and thence toward the supreme cortex…Further, that the tremors excited by the touch of angular bodies in the papillary flesh of the tongue, spread themselves with the sense of taste in a similar manner by their nerves, toward…the cortical substance. And that every ruder touch whatever springs up from the surface of the whole, through the medium of the nerves into the medulla spinalis or medulla oblongata, and so into the highly active cineritious [grey] substance and the circumambient cortex of the brain (Swedenborg 1845–1846).

The cortex, for Swedenborg, has motor as well as sensory function, or in his typically picturesque language:

> The cortical glandule is the last boundary where sensations terminate and the last prison house whence the actions break forth; for the fibres, both sensory and motor, begin and end in these glandules (Swedenborg 1982).

Remarkably, Swedenborg had the idea of the somatotopic organization of motor function in the cerebral cortex. He correctly localized control of the foot in the dorsal cortex (he calls it the "highest lobe"), the trunk in an intermediate site, and the face and head in the ventral cortex (his third lobe):

> …the muscle and actions which are in the ultimates of the body or in the soles of the feet depend more immediately upon the highest parts; upon the middle lobe the muscles which belong to the abdomen and thorax, and upon the third lobe those which belong to the face and head; for they seem to correspond to one another in an inverse ratio (Swedenborg 1982).

There is no other suggestion of the somatotopic organization of motor cortex until the experiments of Fritsch and Hitzig in 1870.

Sources of Swedenborg's ideas on the cortex

Where did Swedenborg's amazingly prescient views come from? There is no evidence that Swedenborg ever carried out any empirical investigations or visited any of the laboratories of the day. Rather his ideas came primarily if not entirely from a careful reading and integration of the anatomical, physiological and clinico-pathological literature that was available to him and that was so copiously quoted in his works (Ramstrom 1910, 1911). He paid particularly close attention to detailed descriptions and observations rather than simply to the authors' own interpretations and conclusions. Furthermore, he was unusual in attempting to integrate observations of the effects of human brain injury with the details of comparative neuroanatomy.

Influence and lack thereof

Swedenborg's writings on religion and spiritualism had an enormous impact on European and American writers and artists. Blake, Yeats, Balzac, the Brownings, Beaudelaire and Strindberg, for example, all claimed to be particularly influenced by him (Jonsson 1971; Toksvig 1848). In nineteenth century America his influence was strong among those interested in spiritualism and in transcendentalism (Novak 1969).

In spite of his fame in literary, artistic and religious circles (or perhaps partially because of it), Swedenborg's ideas on the brain remained largely unknown until the twentieth century. The Latin originals of the *Animal Economy* books of the 1740s were not even mentioned in any of the major physiology textbooks of the following decades (Gross 1997). The English translations of Swedenborg that appeared in the 1840s do not seem to have fared any better. They were ignored in the standard physiology textbooks of the day (Gross 1997).

Early nineteenth century reviews of Swedenborg's biological works were few and puzzled. An *Athenaeum* reviewer in 1844 noted that *The Animal Kingdom* "will startle the physiologist and [contains] many assumptions he will be far from conceding" (Anonymous 1844). The most positive responses seem to have come from books on phrenology (Combe 1852) or mesmerism (Bush 1847).

However, by the time the first volume of Swedenborg's *The Brain* was published in 1882, the Zeitgeist had radically changed. Fritsch and Hitzig (1870) had discovered motor cortex and the race to establish the location of the visual and other sensory cortices was well under way (Gross 1994). Now Swedenborg made sense and both volumes got long rave reviews in *Brain* (Rabagliati 1883, 1888). The reviewer called it "one of the most remarkable books we have seen" and notes that "…it appears to have anticipated some of the most modern discoveries."

Nevertheless, Swedenborg's writings on the brain seem to have disappeared from sight again, not being mentioned in standard physiology or even history of physiology texts.

In 1901 Swedenborg's extraordinary anticipations on the brain were finally publicized by the historian of neuroscience, Max Neuburger, Professor of the History of Medicine in Vienna (Neuburger 1901). As a result, Swedenborg's writings on the brain became the subject of further accounts by neuroanatomists and historians, particularly Swedish ones (e.g. Nordenskiold 1928;Swedenborg Society 1911; Retzius 1908; Ramstrom 1911; Norrving and Sourander 1989). In 1910 a conference of 400 delegates from 14 countries was held in London in honor of his multiple contributions to science, philosophy and theology (Swedenborg Society 1911).

Why was Swedenborg so ignored?

There are several cases of biologists who were so ahead of their time that their writings were read but not understood by their contemporaries, Gregor Mendel being the most famous example (Mayr 1982). Swedenborg's case is more extreme. There is little evidence that contemporary physiologists and anatomists even read his writings on the brain. He never held an academic post or had students, colleagues or even scientific correspondents. He never carried out any systematic empirical work on the brain and his speculations were in the form of baroque and grandiose pronouncements embedded in lengthy books on the human soul by one whose fame was soon to be that of a mystic or madman. Indeed, even he seems to have lost interest in his ideas on the brain, as he never finished or published many of his manuscripts on the subject. Furthermore, some of his more advanced ideas, such as on the organization of motor cortex, did not appear in print until after they were no longer new. As a neuroscientist, Swedenborg failed to publish and as a neuroscientist, he certainly perished.

Curiously, today Swedenborg is a major "outsider" scientist as reflected in books such as: Groll (2000) *Swedenborg and New Paradigm Science*; Jonsson (1999) *Visionary Scientist*: *The Effects of Science and Philosophy on*

Swendenborg's Cosmography; Baker (1992) *Religion and Science*: *From Swedenborg to Chaotic Dynamics*; Dole and Kirven (1997) *Scientist Explores Spirit*: *A Biography of Emanuel Swedenborg;* Toksvig (2007) *Emanuel Swedenborg*: *Scientist And Mystic*; Osgood (2005) *Swedenborg and the Mysticism of Science*; Odhner (1969) *The Human Mind* : *its Faculties and Degrees*: *A study of Swedenborg's Psychology*; Very (2006) *Swedenborg's Science and its Relation to the Science of Today*; Very (2005) *Swedenborg as an Anatomist*.

Claude Bernard and the constancy of the internal environment

Claude Bernard (1813–1878) was the founder of modern experimental physiology and one of the most famous French scientists of all time. Today, the fame of Claude Bernard rests primarily (if not entirely) on his idea that the maintenance of the stability of the internal environment (*miliéu interieur*) is a prerequisite for the development of a complex nervous system. In Bernard's time, his many experimental discoveries in physiology were widely recognized and he received virtually every honor possible for a scientist in France. Yet, his conception of the internal environment had no impact for over 50 years after its formulation (Gross 1998b).

Magendie and the rise of experimental physiology

Bernard had been an indifferent medical student but, somehow, he fell into the hands and laboratory of Francois Magendie (1783–1855), Professor of Medicine at the College de France and head of one of the first laboratories devoted to experimental physiology (Olmsted 1939; Olmsted and Olmsted 1952; Grmek 1970a). Before Magendie, much of physiology had been speculation and inference from anatomy and clinical medicine. Magendie established the importance of direct experiments on living mammals, usually cats, dogs and rabbits (Olmsted 1944; Grmek 1970b; Temkin 1946a). Even after their discovery in the 1840s, anesthetic agents were often not used in animal experiments, perhaps because of their depressing effect on nervous function: in this period experiments on the neural control of physiological function or on the nervous system itself were of central concern. In Magendie's (and Bernard's) time there was much less popular opposition to vivisection in France than in Great Britain; with the rise of a strong British anti-vivisection movement toward the end of the nineteenth century this difference became even greater. In fact, Magendie and Bernard's experiments became grist for the British anti-vivsection movement (Rupke 1987; Schiller 1967; French 1975).

Bernard's experimental achievements

From Magendie, Bernard acquired a profound skepticism of established dogma and learned the techniques of vivisection that were the basis of the new animal physiology. He never practiced medicine and instead concentrated on research, eventually taking over Magendie's laboratory and chair. Bernard made a number of major experimental discoveries and theoretical advances that established him as the founder of modern physiology. Among his most important discoveries were the glycogenic function of the liver, the role of the pancreas in digestion, the regulation of temperature by vasomotor nerves, the action of curare and carbon monoxide on the nervous system, and the vagal control of cardiac function. Most of this work was done early in his career, between 1843 and 1858, in a small damp cellar and with little funding (Olmsted 1939; Olmsted and Olmsted 1952; Grmek 1970a; Robin 1979; Wasserstein 1996).

Bernard was a consistent opponent of vitalism, arguing that biology never violated the laws of physics and chemistry. However, he did stress the emergent properties of complex biological systems much more than his German physiological contemporaries such as Helmholtz and Du Bois Reymond, who strove to reduce biological phenomena to physics and chemistry (Grande 1967; Bernard 1974; Temkin 1946b).

The high point of Bernard's theoretical endeavors was the publication in 1865 of his *Introduction to the Experimental Study of Medicine* (Bernard 1961; Grande 1967). It was an immediate success among scientists and physicians as well as philosophers and writers. Indeed, it remains in print to this day, even in English, and is still heralded as required reading for any prospective experimental biologist. One of its most timeless and attractive aspects is its autobiographical character; Bernard illustrates various principles and practices of experimentation almost exclusively from his own work. He does clean up the stories of some of his discoveries, however, omitting errors, blind alleys, and failed experiments (Grmek 1970a; Holmes 1974). Thus the book makes science seem easier than it really is.

Claude Bernard collected more honors and, arguably, became more famous than any French scientist before or after. From the height of his career until well after his death, Bernard was so famous that he became identified in the public mind as the stereotypical scientist, much like Albert Einstein in the twentieth century (Olmsted 1939; Olmsted and Olmsted 1952; Virtanen 1960). He appears in poetry, memoirs, and novels of the time, both in France and abroad (e.g. "The Brothers Karamazov").

The constancy of the internal environment

Bernard's ideas about the internal environment evolved from its first mention in 1854 until his death in 1878. Initially, for Bernard the internal environment was simply the blood. But even at this stage he understood that the temperature of the blood is actively regulated and that its constancy is particularly critical in higher animals. It was only later that he recognized that this constancy might be achieved through the vasomotor mechanisms he had discovered. At about the same time he realized that the glycogenic mechanism he had found controlled the constancy of blood sugar level. It was primarily on these two (limited) lines of evidence that he built his brilliant generalizations that unify the fundamental physiologies of the body (Holmes 1963, 1967; Langley 1973):

> The fixity of the milieu supposes a perfection of the organism such that the external variations are at each instant compensated for and equilibrated…All of the vital mechanisms, however varied they may be, have always one goal, to maintain the uniformity of the conditions of life in the internal environment…The stability of the internal environment is the condition for the free and independent life (Bernard 1974).

These generalizations both summarized many of Claude Bernard's experimental achievements and provided a program for the next 100 years of general physiology. Although Bernard made these ideas central to his well-attended lectures and his widely disseminated writings, they were ignored in his lifetime and they had no impact at all until about 50 years later. Indeed, Bernard's ideas on the internal environment are hardly mentioned in the extensive 1899 biography by Michael Foster (1899), the distinguished Cambridge physiologist; they are not mentioned at all in the 12-page obituary in the American journal that had published much of Bernard's research (Flint 1878) or in a biographical essay by the eminent historian of science Henry Sigerist (1931). Whereas the 1911 *Encyclopedia Britannica* is totally silent on the constancy of the internal environment, by contrast, the 1975 edition calls it Bernard's "most seminal contribution" (Olmsted 1967; Holmes 1965).

How biology caught up to Bernard's internal environment idea

A contemporary of Charles Darwin, Bernard varied between skepticism and dismissal of Darwinism, reflecting his view that if biological phenomena were not experimentally demonstrable they were of little validity (Grande 1967; Bernard 1974; Virtanen 1960; Petit 1987). Yet, it was only when the profound evolutionary significance of the constitution of the internal environment was realized that Bernard's idea finally had a major impact on physiology.

The development that catalyzed the understanding of Bernard's milieu interieur was the comparison of the ionic concentrations of body fluids with those of sea water (Holmes 1965). In 1882 Leon Fredericq observed that the body fluids of ocean crabs, lobsters and octopuses were about as salty as seawater, whereas marine fish, like fresh water ones, were much less salty. He realized that this was the first evidence for Bernard's idea that the internal milieu becomes increasingly independent of the external environment as one ascends the "living scale," thereby providing the basis for the "free life" of higher organisms (Holmes 1965; Fredericq 1973). Fredericq had studied in Paris with Paul Bert, a major student, collaborator, and biographer of Bernard. In marked contrast to Bernard, however, Fredericq interpreted his comparative observations as evidence for the evolution of the independence of the internal environment from the external one.

By the end of the century, evolutionary thinking had finally made the constituents of the internal environment a meaningful subject. Independently. Rene Quinton and Archibald Macallum took the next step, arguing that life arose in the sea and that body fluids represented the original seawater that had been enclosed within the skin. More generally, it became clear that a major trend in evolution was the development of increasingly sophisticated mechanisms whereby the internal environment is protected from the external world (Petit 1987; Macallum 1926).

In the first decades of the twentieth century, Bernard's ideas about the importance of the internal environment entered the mainstream of mammalian physiology both as a central explanatory concept and a program for research (Gross 1998b). Among the major British figures explicitly relating their work closely to Bernard's idea were William Bayliss and E.H. Starling, co-discoverers of secretin, the first hormone identified; J.S. Haldane (J.B.S. Haldane's father) and Joseph Barcroft, pioneers in the regulatory functions of breathing; and C.S. Sherrington, a founder of modern neurophysiology. Starling seconded Macallum and Quinton's ideas on the evolution of the internal environment and later coined the term "the wisdom of the body" for the maintenance of the internal constancies that Bernard had postulated (Starling 1909). Barcroft claimed that the "principles…of the fixity of the internal environment have been as thoroughly established as any" (Barcroft 1932). Haldane noted that Bernard's conception "sums up and predicts" his own work on the regulation of blood composition by respiration (Haldane 1931). Sherrington suggested that "the nervous system is the highest expression of…the milieu intérieur" (Sherrington 1961).

In the United States the chief advocates of Bernard's constancy ideas were L.J. Henderson and Walter B. Cannon,

long-time members of the Harvard Medical School faculty. Henderson related his work on the maintenance of blood pH directly to Macallum's marine biology as well as to Bernard. He helped bring Bernard to a wider American audience both in his introduction to the American translation of Bernard's *Introduction* and in his own influential book, *The Fitness of the Environment* (Henderson 1958, 1961).

Walter B. Cannon was particularly instrumental in making Bernard's ideas central to the neurophysiology and psychology of the time. He coined the term "homeostasis" for the tendency of the mammalian organism to maintain a constant internal environment (Cannon 1929). His own major discoveries were in elucidating the role of the sympathetic nervous system in maintaining homeostasis; he brought these to the educated public in the classic *The Wisdom of the Body* (Cannon 1963a). Cannon viewed behavior as a homeostatic mechanism: shivering, seeking shelter and putting on a coat were all examples of homeostatic mechanisms of temperature regulation. J.B. Watson and other early behaviorists such as Curt Richter rejected the myriad of previously postulated central drives as explanations for motivation. They turned instead to the experiments of Cannon for alternative and peripheral mechanisms of motivation and considered "motivated" behavior as a homeostatic mechanism. Thus, following him, they viewed thirst as due to dryness in the mouth, which, when signaled to the brain, elicited drinking. Similarly, hunger was caused by stomach contractions ("pangs") which signaled the brain to elicit eating. Extrapolating beyond Cannon, they interpreted sexual motivation as due to tension in the gonads (Watson 1930; Richter 1927; Cannon 1963b).

Both Cannon and Henderson had extended Bernard's ideas of self-regulation from the realm of bodily fluids to the wider social environment (Cannon 1963a; Henderson 1935). The idea of self-regulation was extended even further to include the non-biological world by Arturo Rosenblueth (one of Cannon's collaborators), Norbert Weiner and J. Bigelow (Rosenblueth et al. 1943). In the context of World War II control and communication systems, they pointed out that negative feedback covered self-regulation both in the nervous system and in non-living machines. Soon after, Weiner coined the term "cybernetics" for "the entire field of control and communication theory, whether in the machine or in the animal" (Wiener 1961). Today, cybernetics, a formalization of Bernard's constancy hypothesis, is viewed as one of critical antecedents of contemporary cognitive science (Gardner 1985).

Why the delay?

Despite the emphasis with which he repeatedly promulgated it, Claude Bernard's insight that the "constancy of the internal environment is the condition for the free life" had no significance, indeed, no meaning for biologists for over 50 years. There appear to have been several reasons for this inability to process his idea. One was that Pasteur's new bacteriology and its omnipresent, omnipotent germs were dominating the biomedical Zeitgeist. Another, as discussed above, was the gap between evolutionary thought and general physiology. When this gap began to be closed through the comparison of the constituents of seawater and the bodily fluids at different phylogenetic stages, the constancy of the internal environment suddenly took on new and accessible meaning. Finally, the tools, techniques and concepts for adequately measuring the internal environment were simply not available in Bernard's time and for the rest of the century. For example, the work of Haldane, Henderson and Barcroft required the development of organic and especially physical chemistry, as well as techniques for measuring ions, gases and other components of the internal environment; the work of Sherrington and Cannon required the replacement of the reticular doctrine by the neuron doctrine, and the development of the cathode-ray oscilloscope and electrical stimulating devices (Virtanen 1960; Olmsted 1967; Holmes 1965).

Unlike Emmanuel Swedenborg, who was so far ahead of his time that he died unrecognized for his ideas on brain function, Claude Bernard, by contrast, received every possible recognition as a scientist and yet what is today considered his most salient contribution had to wait half a century for advances in theory and practice to make it meaningful (Gross 1998b).

Joseph Altman and adult neurogenesis

The dogma of no new neurons in the adult mammalian brain

From the beginning of the Neuron Doctrine in the late nineteenth century to the early 1990s a central dogma in neuroscience was that "no new neurons are added to the adult mammalian brain" (Ramón y Cajal 1928; Rakic 1985a, b; Jacobson 1970). By the end of the nineteenth century, the idea that the brain of the adult mammal remains structurally constant was already universally held by the neuroanatomists of the time. Koelliker, His and others had described in detail the development of the central nervous system of humans and other mammals (Koelliker 1896; His 1904; Ramón y Cajal 1999). They found that the structure of the brain remained fixed from soon after birth. Because the elaborate architecture of the brain remained constant in appearance, the idea that neurons were continually added to it was, understandably, inconceivable. Similarly, Ramón y Cajal and others had described the different phases in the development of the neuron, terminating with the multipolar

structure characteristic of the adult (Ramón y Cajal 1928, 1999. As neither mitotic figures nor pre-adult developmental stages had been seen in the adult brain, the possibility of continuing neuronal addition to the adult brain was rarely, if ever, seriously entertained. As (Ramón y Cajal 1928) put it "In the adult centers the nerve paths are something fixed, ended and immutable. Everything may die, nothing may be regenerated".

In the first half of the twentieth century, there were occasional reports of postnatal neurogenesis in mammals but these were usually ignored by textbooks and rarely cited (see Gross 2000). Presumably this was because of the weight of authority opposed to the idea and the inadequacy of the available methods both for detecting cell division and for determining whether the apparently new cells were glia or neurons (Ramón y Cajal 1928).

Altman challenges the dogma and is ignored

An important advance in the study of neurogenesis came in the late 1950s with the introduction of [H^3]-Thymidine autoradiography. [^{3}H]-Thymidine is incorporated into the DNA of dividing cells. Therefore, the progeny of cells that had just divided could be labelled, and their time and place of birth determined. Initially, this new method was applied exclusively to the study of developing rodents (Sidman et al. 1959). The emphasis on using this method to study pre- and peri-natal development, rather than looking across the life span of the animal, reflected the persistence of the belief that neurogenesis did not occur in the adult mammal.

Starting in the early 1960s, Joseph Altman (1925–) challenged this idea of "no new neurons in the adult brain". He published a series of papers (Altman 1962, 1963; Altman and Das 1965, 1966a, b; Altman 1967, 1969) reporting thymidine autoradiographic evidence for new neurons in the dentate gyrus of the hippocampus, the olfactory bulb and the cerebral cortex of the adult rat (Altman 1969). He also reported new neurons in the neocortex and elsewhere in the adult cat (Altman 1963). Most of the new neurons were small and he suggested that they were crucial for learning and memory (Altman 1967). Although published in the most prestigious journals of the time, such as the *Journal of Comparative Neurology*, *Science* and *Nature*, these findings were totally ignored or dismissed as unimportant for over two decades.

Altman was not granted tenure at MIT and moved to Purdue University where he eventually turned to more conventional developmental questions (Altman and Bayer 1995), perhaps because of the lack of recognition of his work on adult neurogenesis. Unable to get grants he supported his work by producing magnificent brain atlases (e.g Altman and Bayer 1995, 1996; Bayer and Altman 2007) As late as 1970, an authoritative textbook of developmental neuroscience (Jacobson 1970) stated that "…there is no convincing evidence of neuron production in the brains of adult mammals".

Kaplan confirms Altman and is also ignored

Fifteen years after Altman's first report, direct support for his claim of adult neurogenesis came from a series of electron microscopy studies by Michael Kaplan and his coauthors. First, they showed that [^{3}H]-thymidine labelled cells in the dentate gyrus and olfactory bulb of adult rats have the ultrastructural characteristics of neurons, such as dendrites and synapses, but not of astrocytes or oligodendrocytes (Kaplan and Hinds 1977; Kaplan 1984). Then (Kaplan 1981, 1984) reported autoradiographic and ultrastructural evidence for new neurons in the cerebral cortex of adult rats, again confirming the earlier claims of Altman (Altman 1963; Altman and Das 1966b). Finally, he showed mitosis in the subventricular zone of adult macaque monkeys by again combining [^{3}H]-thymidine labeling and electron microscopy (Kaplan 1983). During this period, Kaplan was, successively, a graduate student at Boston University, a post-doctoral fellow at Florida State University and an assistant professor at the University of New Mexico. Attacked for his iconoclastic claims, Kaplan left the field, became a medical student and now works in rehabilitation medicine (Kaplan 2001). In spite of his evidence for adult neurogenesis, Kaplan's work had little effect at the time, as measured by citations or follow-up studies. Again, as in Altman's case, publication in prestigious and rigorously reviewed journals, such as *Science*, the *Journal of Comparative Neurology* and the *Journal of Neuroscience*, by an unknown figure was not sufficient to make any marked dent in the dogma.

An important reason for the small impact of Kaplan's work may have been a study presented at a meeting in 1984 and published the following year (Rakic 1985a, b). Pasko Rakic, the author of the study, was (and still is) Professor at Yale Medical School and arguably the leading student of primate brain development. He carried out a [^{3}H]-thymidine study of adult rhesus monkeys in which he examined "all major structures and subdivisions of the brain including the visual, motor, and association neocortex, hippocampus, olfactory bulb". Rakic found "not a single heavily labelled cell with the morphological characteristics of a neuron in any brain of any adult animal" and concluded that "all neurons of the rhesus monkey brain are generated during prenatal and early postnatal life" (Rakic 1985a, b).

Rakic's (1985a, b) papers had a profound influence on the development of the field. Subsequent work in adult rhesus monkeys by (Eckenhoff and Rakic 1988), using a combination of thymidine autoradiography and electron microscopy also failed to find new neurons in the adult.

Furthermore, the authors questioned the reports of adult neurogenesis in rats with the suggestion that rats never stop growing and so never become adults. (In fact, there are strains of rats that do stop growing and also show adult neurogenesis (Boss et al. 1985; Kuhn et al. 1996) but this was not known at the time.) For Eckenhoff and Rakic, the supposed lack of adult neurogenesis in primates made sense, because, "a stable population of neurons may be a biological necessity in an organism whose survival relies on learned behavior acquired over a long period of time". Furthermore, Rakic 1985a suggested that the "social and cognitive behavior" of primates may require the absence of adult neurogenesis.

Humans often show a basic need to distinguish themselves from other animals (Gross 1993) and sometimes primates from other animals on cognitive grounds. Although neuroscientists have often tried to make these distinctions in terms of brain structure or function (Gross 1993), Rakic's suggestion may be the only time that the social and cognitive differences between primates and non-primates was attributed to the presence or absence of adult neurogenesis and, more generally, to the structural stability of the brain.

There were three developments that led to a vindication of Altman's pioneering work and general acceptance that new neurons are added to the adult mammalian brain and that this was probably an interesting and important phenomenon. The first development was the demonstration of neurogenesis in adult birds. The second was the introduction of new methods for labeling new cells and for distinguishing neurons from glia. Finally, demonstrations that neurogenesis could be up-and downregulated by important psychological variables such as stress, environmental complexity and learning, raised the possibility that adult hippocampal neurogenesis might be important for cognition in higher animals.

Avian neurogenesis

Starting in the late 1980s, Nottebohm and his colleagues at Rockefeller University began a systematic analysis of the neural basis of song learning in birds. They discovered a set of brain mechanisms that are crucial for bird song and showed how the volume of two nuclei were a function of variables such as sex, sexual maturity, song complexity, species, testosterone level and season (Nottebohm 1985, 1989). The seasonal and hormonal changes in the volume of these song-related nuclei were so great in some species that Nottebohm set out to examine the possibility that these changes were due to fluctuations in the actual number of neurons in the adult avian brain.

In a series of elegant experiments, Nottebohm and his colleagues showed that, indeed, thousands of new neurons are added every day to the avian brain. They did so by, first, showing the production of new cells with thymidine labeling (Goldman and Nottebohm 1983); second, producing ultrastructural evidence that the new cells were neurons receiving synapses (Burd and Nottebohm 1985); and last, in a technical tour de force, showing that the putative neurons responded to sound with action potentials (Paton and Nottebohm 1984). In subsequent studies, they showed that the axons of new neurons extended over long distances, that neuronal birth and death proceeded in parallel, that in both singing and non-singing species neurogenesis was widespread throughout the avian forebrain—including the hippocampus—and that in the latter structure it was modulated by environmental complexity and learning experience (Nottebohm 1985, 1989, 1996; Goldman and Nottebohm 1983; Burd and Nottebohm 1985; Paton and Nottebohm 1984; Barnea and Nottebohm 1994, 1996; Kirn and Nottebohm 1993).

In spite of this unassailable evidence of neurogenesis in parts of the adult bird brain known to be homologous to primate cerebral cortex and primate hippocampus, these studies tended to be viewed as irrelevant to the primate or even the mammalian brain. Rather, the evidence for avian neurogenesis was viewed as an exotic specialization related to the necessity for flying creatures to have light cerebrums and to their seasonal cycles of singing.

New techniques

Beginning around the 1990s, there were several developments that finally established the reality of neurogenesis in the dentate gyrus of the adult rat. One was the demonstration that the new cells in the rat dentate gyrus extend axons into the mossy fiber pathway (Stanfield and Trice 1988).

The second important development was the introduction of the synthetic thymidine analogue BrdU (5-bromo-3′-deoxyuridine). Like thymidine, BrdU is taken up by cells during the S-phase of mitosis and is a marker of proliferating cells and their progeny. BrdU labelling can be visualized with immunocytochemical techniques and does not require autoradiography (Nowakowski et al. 1989). More recently, an endogenous marker for cell proliferation, Ki-67, was been introduced. Ki-67 is a protein that is a cellular marker for cell proliferation. It is present during mitosis but is absent in the resting cell (Scholzen and Gerdes 2000).

Perhaps the most important advance was the use of cell-type specific markers enabling the immunohistochemical distinction of the newly generated neurons from glia cells. Among the markers for mature neurons are NSE, MAP-2, TuJ1 and NeuN. Although some of these markers have been shown to stain non-neuronal cells under certain conditions and others do not stain all neuronal types (Mullen et al. 1992; Deloulme et al. 1996; Sensenbrenner et al.

1997; Rosser et al. 1997), the expression of several of these antigens in a population of adult-generated cells is considered good evidence that new neurons have been produced. There are also markers for immature neurons and for glia (oligodendrocytes and astrocytes). The combination of BrdU for detecting new cells with immunochemical markers for neurons now allowed the identification of new neurons.

Regulation of neurogenesis

The advent of these new techniques meant that by the 1990s, Altman's claim that new neurons were added to the adult dentate gyrus had been confirmed several times (Cameron et al. 1993; Seki and Arai 1995; Kuhn et al. 1996; Abrous et al. 2005) and by now is well established for a variety of mammals including humans (Eriksson et al. 1998) and other primates (Gould et al. 1998, 1999).

But was this phenomenon more than some ontogenetic lag or phylogenetic vestige? At least in rats the number of new hippocampal cells is so large, over 9,000 cells per day, most of which are neurons, makes this very unlikely (Cameron and Mackay 2001). Furthermore, dentate gyrus neurogenesis in the rodent can be modulated by a number of experiential variables and so might be important for cognitive function (Abrous et al. 2005; Gould 2006). For example, acute and chronic stress decreases hippocampal neurogenesis. Adrenal steroids probably underlie this effect as stress increases adrenal steroid levels and glucocorticoids decrease the rate of neurogenesis. By contrast, there are several conditions that increase the number of adult-generated dentate gyrus cells, environmental complexity and wheel running being particularly well-studied enhancers of adult neurogenesis.

In Altman's earliest studies he speculated that adult neurogenesis might play a crucial role in learning and memory (Altman 1967). In recent years this idea had been subjected to an increasing amount of experimental examination. Although there are conflicting results, the preponderance of evidence supports Altman's speculation: the number of new neurons often positively correlates with learning of hippocampal dependent tasks, learning such tasks tends to increase the number of new neurons and the depletion of new hippocampal neurons is reported to impair hippocampal dependent learning (Leuner et al. 2006; Abrous et al. 2005).

Adult neurogenesis in the olfactory bulb and cerebral cortex

At about the time as Altman's finding of neurogenesis in the dentate gyrus was confirmed, his report of neurogenesis in the adult olfactory bulb was also replicated (Lois and Alvarez-Buylla 1994; Corotto et al. 1994). Neurogenesis in the adult olfactory bulb has now been shown for a variety of mammals, including humans (Curtis et al. 2007), and, at least, in rats is modulated by olfactory experience and learning (So et al. 2008; Mandairon et al. 2006).

The status of Altman's report of adult neurogenesis in the cerebral cortex is less clear. Beyond Altman and Kaplan's work, a number of investigators have reported cortical neurogenesis in the hamster, rat, marmoset and macaque cortex. However, others have failed to find cortical neurogenesis. Gould (2007) and Cameron and Dayer (2008) have reviewed the positive and negative studies and suggested that the negative results were due to insufficient sensitivity of the methods used and the small number and size of the new cortical neurons.

Why were Altman's discoveries ignored for almost 30 years?

There appear to be several reasons why Altman's discovery of neurogenesis in the hippocampus and the olfactory bulb were ignored. First, there were not accessible and reliable techniques for the objective differentiation of small neurons from glia, particularly astrocytes. Until the 1990s this distinction could only be made by "an expert eye" and almost by definition, "experts knew" that adult neurogenesis did not occur in mammals Another reason was that Altman, although in a leading university (MIT), was at the time of his early adult neurogenesis papers a self-taught post-doctoral fellow in a psychology department and had not been trained in a distinguished, or indeed, any developmental laboratory or one using autoradiographic techniques. Finally, the dogma of "no new neurons" was universally held and vigorously defended by the most powerful and leading primate developmental anatomist of his time.

The continued resistance to acceptance of neurogenesis in the adult cerebral cortex may be due, in part, to the much lower incidence of cortical neurogenesis than hippocampal neurogenesis and therefore the greater importance of sensitive methods for detecting new neurons there. It may also reflect the continued investment of more traditional members of the community in denying neuronal plasticity.

The three cases

There were both common elements and ones that were very different in the neglect by their contemporaries of Swedenborg's ideas on the brain, Bernard's dictum on the constancy of the internal environment and Altman's discovery of neurogenesis.

Swedenborg and Altman faced impregnable ideological resistance, for Swedenborg, the dogma that the cortex was a

functionless rind and for Altman the dogma of no new neurons.

Swedenborg's publications never reached the scientific community whereas both Bernard's and Altman's were very widely available.

Bernard was the most famous French scientist of his time (and arguably, all time), whereas Swedenborg was not even recognized as a biologist.

All three had ideas that were difficult or impossible to test in their own time.

It took over 150 years for Swedenborg to be rediscovered, Bernard's ideas on the internal milieu about 50 years and Altman's adult neurogenesis only about 30 years.

They were all iconoclasts and their icons were resilient.

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