

## Section 1

## Introduction

## Chapter

## 1

**Historical introduction: the causes of epilepsy in the pre-molecular era (1860–1960)**

– from John Hughlings Jackson to William Lennox

Simon D. Shorvon

The evolution of theories of etiology in epilepsy makes an interesting study at many levels: some theories reflect social and philosophical attitude; some, widely believed and extensively written about at the time, have proved totally erroneous and now even appear ridiculous; and others show scientific insight now lost and worth reappraisal. Much can be learned also from the constructs with which our predecessors conceptualized the process of epilepsy, not least because it puts into perspective our current thought. In this chapter, the theories of etiology for the 100 years since the time of John Hughlings Jackson, whose writing has often been said to announce the dawn of modern epileptology, will be outlined. The chapter ends with William Lennox, a natural break as in many ways Lennox sums up the work of the previous century. After Lennox, the new molecular biology, imaging, and genetic techniques have proved powerful tools in the exploration of etiology and have greatly changed our understanding in the field. Nevertheless, some concepts and ideas of the pre-Lennox period have resonance today and are worth re-evaluation.

In earlier times, epilepsy was almost universally considered to be the result of supernatural or magic forces, or possession by evil spirits or the devil. Leading medical thinkers repeatedly rounded on such superstitious explanations; Hippocrates wrote for instance both that epilepsy was an organic disease of the brain and that “its origin is hereditary, like that of other diseases.” Galen divided epilepsy into three etiological groups (remarkably analogous to theories prevalent today): a dyscrasia of the humors of the brain; a stimulation of the brain by an irritating substance brought into the brain from the body (the convulsion being the brain’s efforts to repel the irritant); and the invasion of the brain by a pathological humor formed in the extremities. Nevertheless, despite these physical explanations, the majority of physicians and of the public continued to accept supernatural theories right up to the mid nineteenth century and a few continue to do so. In the early nineteenth century, other theories of etiology began to take shape, not least those revolving around heredity. This earlier history is well

described by Temkin (1945), whose detailed survey ends in large part in the mid nineteenth century. This chapter starts at this point, when the modern age of epileptology can be said to have been entered.

**Theories of the causation of epilepsy 1860–1907****Concepts of etiology in the mid nineteenth century**

In the middle of the nineteenth century, there was a recrudescence of interest in epilepsy and its causes, particularly in neurological circles. A number of influential books were written, especially by the English neurologists, which demonstrate a more clinical and physiological view than was previously the case. The first of these books, *Epilepsy and Epileptiform Seizures*, by Edward Sieveking (1861) (Fig. 1.1) provides an interesting starting point for our survey, representing as it does a transition to modern thought. His discussion of etiology starts with a consideration of demonic possession, which he dismisses. The “causes of epilepsy” are divided into “predisposing and exciting components,” a common formulation of the period, and Sieveking articulated what was a predominate theory of the time, that the predisposing causes were largely inherited, and formed the *epileptic diathesis*, which he defined using the following rather vivid analogy: “Diathesis may be compared to combustible material of greater or less inflammability, which differs in the facility with which it will take fire, but will infallibly do so if a flame of sufficient intensity is brought into contact with it” (Sieveking 1861). Amongst the predisposing causes, he found “hereditary influences are very palpable” and cites Herpin who “amongst 68 patients with epilepsy found 78 relatives who laboured under some affection of the nervous system” (Table 1.1). The diathesis was embedded in the concept of the “neurological taint,” a theory of great influence at the time, and of which more below. However, other mechanisms were also evident to Sieveking who discoursed lengthily on albuminuria, but particularly constipation and other derangement of the bowels. He also emphasized

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**Fig. 1.1.** Sir Edward H. Sieveking (1816–1904), appointed physician to the National Hospital Queen Square in 1864.

the importance of sexual disturbances as a cause of epilepsy, both predisposing and exciting: “Although the unanimous consent of all writers on epilepsy demonstrates the truth of the statement that in this disease, the sexual organs are very frequently at fault ... it is by no means determined in how far sexual derangements are to be regarded as a predisposing or exciting cause” and he then cites the ancient proverb attributed to Galen: “*coitus brevis epilepsia est.*” He believed that sexual derangement “enfeebled the system, and by producing excitability gives rise to the epileptic paroxysm.” Masturbation was a particular cause, and Sieveking wrote that in nine of 52 of his cases, he found “the sexual system was in a state of great excitement, owing to recent or former masturbation.” The theory that sexual practices predisposed to epilepsy was one held by many earlier authors and was again widely but not universally held at this time. Sieveking noted that the influence of the menstrual cycle was most important in females and masturbation in males (evidence of the latter in 31%). Interestingly Sieveking makes no mention of “degeneracy,” nor of Morel whose work was published contemporaneously, reflecting the then divergent paths of British and Continental epileptology (see below).

### J. Russell Reynolds

In the same year that Sieveking’s book appeared, Reynolds (Fig. 1.2), another leading London neurologist, knighted and awarded an FRS, published his book *Epilepsy: Its Symptoms, Treatment and Relation to Other Chronic Convulsive Diseases* (Reynolds 1861) which became extremely influential. Jackson,

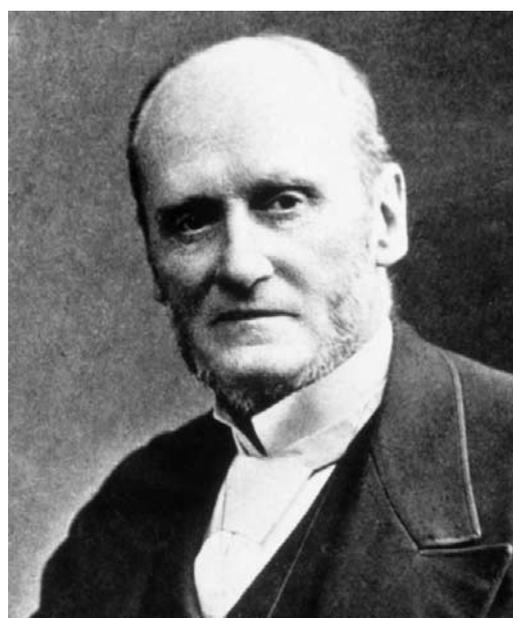
**Table 1.1** Associated neurological conditions in 380 relatives of 68 epileptics

Epilepsy	10
Insanity	24
Suicide	1
Melancholia	2
Hypochondriasis	3
Hysteria	2 <sup>a</sup>
Chorea	2
Sleepwalking	2
Nervous excitability	3
Apoplexy	11
Cerebral softening	1
General paralysis	2
Meningitis and chronic hydrocephalus	13
Mortal convulsions	1
Tetanus	1
Total	78

Note:

<sup>a</sup>I cannot but demur to this number, and it is incredible that not more than two relatives of 68 epileptics should have been hysterical.

Source: From Herpin, cited by Sieveking (1861).



**Fig. 1.2.** Sir J Russell Reynolds FRS (1828–96) was physician to the royal household and President of the Royal College of Physicians, and physician at the National Hospital Queen Square from 1864.

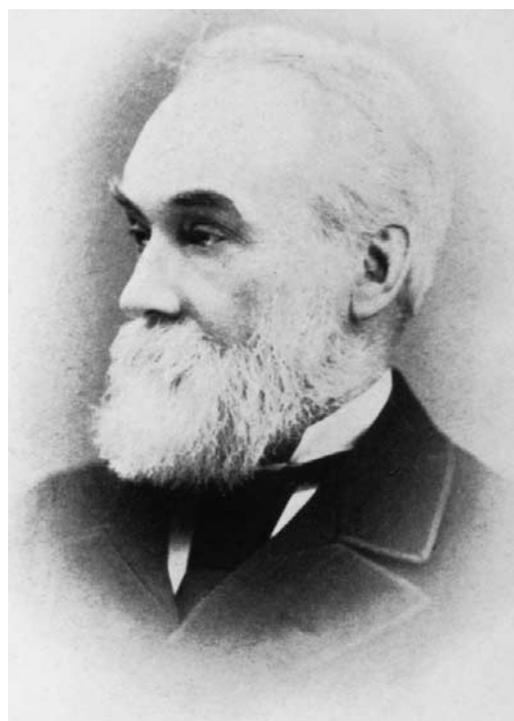
for instance, extensively cites the book and Gowers dedicated his own book of 1888 to Reynolds (“whose example stimulated and friendship encouraged”). Reynolds considered the “causes

**Table 1.2** The classification of epilepsy devised by J. Russell Reynolds (1861)

Category	Comment
1. Idiopathic epilepsy	An internal cause – a <i>morbus per se</i> . This may have a basis in heredity or conditions operating after birth.
2. Eccentric epilepsy	Epilepsy due to some systemic disturbance which when cured will result in the cessation of seizures. Reynolds accepted that “eccentric convulsions” can be exacerbated by a predisposing tendency, and he proposed that they had a “reflex” basis.
3. Diathetic epilepsy	Epilepsy in which the convulsions are primarily due to cachexia or toxemia, and in which the nervous system is “involved in that general nutrition-change which is the essential element of the cachexia itself” and have their basis in a general not specific remote causes. These can include patients with an existing predisposition (or not) and other existing symptomatic causes.
4. Symptomatic epilepsy	Epilepsy in which convulsions are due to “more or less contiguous structural disease of the brain. Thus, an intracranial tumor, a chronic inflammatory condition of the meninges, softening or disintegration of the brain substance, or any other structural change in the nervous centres ... may set up that peculiar interstitial or molecular change which is the immediate cause of convulsion.”

of epilepsy” to be divided into proximate and remote categories. The proximate cause is the same in all cases – an abnormal increase in the nutritive changes of the nervous system (a similar concept to the current emphasis on excitatory changes). He recognized that the remote causes may be very slight in some cases, and in others severe remote disease resulted in very insignificant epilepsy, that there were diverse remote causes but all were mediated through this defect of nutrition, and that the different forms of seizure were due to differing anatomical locations of the abnormal nervous centers – in all this, he anticipated Jackson.

He classified epilepsy into four categories, an excellent scheme worth recording here for its lessons for today’s nosologists (Table 1.2). In his category of idiopathic epilepsy, he included other inherited conditions of the neuropathic taint (see below), including mania, idiocy, paralysis, and insanity. He considered an inherited influence was present in 31% of his own cases. The category of “eccentric” epilepsy is very similar to our current concept of “acute symptomatic seizures” and Reynolds listed causes which included teething, worms, and poisons. Diathetic epilepsy seems to be a new category, in which the nutritive change is not confined to the brain but is part of the general systemic disturbance caused by toxemia or cachexia. The causes of cachexia he listed included: tuberculosis,

**Fig. 1.3.** John Hughlings Jackson FRS (1835–1911), the father of modern epileptology, was physician at the National Hospital Queen Square from 1862 to 1906.

scrophula, rachitis, syphilis, pyemia, anemia, alcoholism, lead poisoning, typhus, variola, and other exanthemata and diseases which alter nutrition such as pneumonia, carditis, and pericarditis. The term “symptomatic epilepsy” was reserved for epilepsies in which there was a contiguous structural brain disease, a term similar but more narrow than the usage today.

Reynolds viewed the manifestations of epilepsy as the summation of disturbances of structure and function, and considered that the proximate and remote causes cannot be separated from the disease itself.

It is also notable that Reynolds considered that an emphasis on masturbation to be mistaken, and that the ideas of “some mysterious entity taking possession of the body” a theory “long since passed.” This then was the state of advanced thinking on etiology at the start of our period, when John Hughlings Jackson began to publish his work on epilepsy.

## John Hughlings Jackson

The works of John Hughlings Jackson (Fig. 1.3) are generally agreed to have laid the foundations for much of modern epilepsy studies. An enormous contribution was his observation that “a convulsion is but a symptom, and implies only that there is an occasional, an excessive, and a disorderly discharge of nerve tissue on muscles” (1873). In his Lumlian lectures of 1890, he defined nervous discharge as the liberation of energy by nervous elements and the epileptic discharge as sudden, temporary and excessive in nature, a kind of explosive

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discharge ... it was “the physiological fulminate” like the gunpowder in a cannon, and just as gunpowder can store energy that is liberated when firing the gun, so the energy stored in nerve cells could be explosively liberated in an epileptic discharge. This definition of epileptic seizures has remained central, ever since, to all thought on the condition and was a quite remarkable insight. The reason for the abnormal levels of stored energy was deranged “nutrition” in Jackson’s view. He equated “cause” with “causal mechanism” and was in general not particularly interested in the question of etiology in the sense usual today; his focus was on theories of physiology. The only sustained piece of writing on causation was in his paper, published in 1874, entitled “On the scientific and empirical investigation of epilepsies” (Jackson 1874, pp. 162–273). He wrote that:

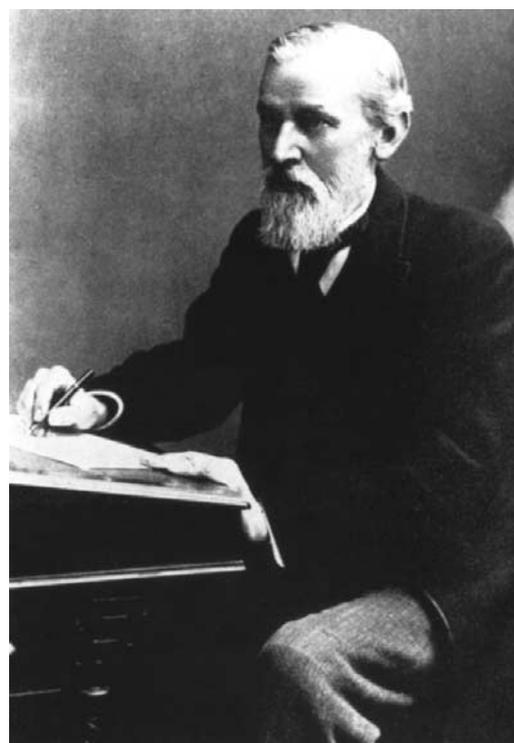
The confusion of two things physiology and pathology under one (pathology) leads to confusion in considering “causes”. Thus, for example, we hear it epigrammatically said that chorea is “only a symptom” and may depend on many causes. This is possibly true of pathological causation; in other words it may be granted that various abnormal nutritive processes may lead to that functional change in grey matter which, when established, admits occasional excessive discharge. But physiologically, that is to say, from the point of view of Function, there is but one cause of chorea – viz. instability of nerve tissue. Similarly in any epilepsy, there is but “one cause” physiologically speaking – viz. the instability of the grey matter, but an unknown number of causes if we mean pathological processes leading to that instability.

Jackson defined the term *physiology* in the narrow and specific meaning of:

the departure of the healthy *function* of nerve tissue. That function is to store up and to expend force ... in epilepsy, the cells store up large quantities and discharge abundantly on very slight provocation: there is what I call instability, or what is otherwise spoken of as increased excitability.

By the term *pathology* he meant “disordered nutrition” and in epilepsy (and excessive discharge) the pathological process was overnutrition which, in Jackson’s view, was often caused by congestion of small blood vessels following occlusion of other vessels. He did recognize that there were many possible contributing factors that may result in the vascular disturbance (and thus in overnutrition and thus in the discharge) and those that he mentioned were tubercle, cicatrix, tumor, syphiloma, or hemorrhagic or ischemic stroke. He also realized that there was often no visible cause. His discussion of etiology, though, was not on these conditions but on the nutritional and vascular disturbances itself. He also recognized, *pari passu*, that the position and hierarchical level of the discharging tissue in the nervous system determined the form of the epilepsy.

In summary, Jackson makes the novel and important point that in epileptogenic tissue, the nervous centers are hyperexcitable and that the mechanism by which external or internal factors result in an epileptic seizure is similar and mediated via vascular congestion resulting in metabolic changes in the cells



**Fig. 1.4.** Sir William Gowers FRS (1845–1915) was appointed physician to the National Hospital Queen Square in 1872.

(he defines this mechanism as “the cause of epilepsy”). Many different disease entities can result in this vascular imbalance, but this was not his focus. Furthermore, he held that predisposing factors such as heredity “set” the level of hyperexcitability in individual cases and determine the response of tissue to the stimulus of overnutrition. Like Reynolds and others before him, Jackson really only considered “idiopathic” epilepsy to be true epilepsy, and other forms (symptomatic or organic epilepsies) from the point of view of causation to be worthy of little specific study.

## William Gowers

The next important published work on epilepsy was Sir William Gowers’ famous book, *Epilepsy and Other Chronic Convulsive Diseases* (Gowers 1881), the first edition of which was published in 1881 with a second edition in 1901, and his views were summarized in this and in his famous and gigantic textbook of neurology of 1888 (*A Manual of Diseases of the Nervous System*; Gowers 1888). Gowers (Fig. 1.4) took a much more empirical approach to causation than Jackson. He classified epilepsy into idiopathic epilepsy and organic epilepsy, and considered only idiopathic epilepsy to be “true epilepsy.”

The first chapter of his book was devoted to the causes of idiopathic epilepsy. He divided these into two types, *predisposing* causes and *exciting* causes, the former being “remote” and the latter “immediate” (interestingly a different usage than that of Reynolds for instance). The analogy of gunpowder was used

by Gowers (following Sieveking and Jackson) – the gunpowder being the predisposing cause and the spark the exciting cause. It is interesting to note that the terms “eccentric” and “diathetic,” used by Reynolds, do not appear in Gowers’ book, and his use of the term “reflex” has also changed.

Of the predisposing causes, by far the most important was “heredity.” As Gowers put it, “there are few diseases in the production of which inheritance has more manifest influence.” The concept of the “neuropathic trait” (the neuropathic tendency; see below) had taken a strong hold by then, and heredity was widely defined. As Gowers wrote:

It is well known that the “neuropathic tendency” does not always manifest itself in the same form, but is not easy to discern the relation of its varieties . . . The chief morbid states (besides epilepsy itself) by which the same neuropathic tendency is manifested is insanity, and, to a much smaller degree, chorea, chronic hysteria, migraine, and some chronic forms of disease of the brain and of the spinal cord. Intemperance is probably also due, in many cases, to a neuropathic disposition.

Of 2400 cases investigated by Gowers, 40% had an inherited tendency in his view, and his later series had even higher rates. Gowers went on to say that, because of the neuropathic trait, epilepsy and insanity were almost interchangeable terms, with three-quarters of those with inherited insanity also having epilepsy. Other predisposing causes were age (74% of epilepsy developed in Gowers’ series before the age of 20 years), sex (female cases are greater in number; 52% of 2000 cases in Gowers’ series), and inherited syphilis but not other (indirect) inherited conditions such as rheumatism, phthisis, and gout (a common theory at the time). Consanguinity was considered to intensify existing tendencies and only to play a significant part in epilepsy when “neurotic heredity exists in both parents.”

The exciting causes in idiopathic epilepsy were, in Gowers’ opinion, secondary in importance to inherited causes:

It may be again pointed out, to prevent misconception, that these exciting causes cannot be regarded as the essential causes of the disease except in a very small number of cases . . . The real cause of the disease is the morbid state of the nervous system.

Of 1665 cases, Gowers considered that a reasonable exciting cause could be found in 42% (696 cases). These exciting causes included: difficulty with labor, birth trauma, febrile convulsions (teething fits), rickets, organic lesions of the brain, mental emotion (fright, excitement, anxiety), acute diseases (measles, scarlet fever, typhus, typhoid, rheumatic fever, influenza, diarrhea), reflex seizures, asphyxia, lead poisoning, renal disease, anesthetics, disturbed menstruation, pregnancy, and syphilis. Gowers was doubtful about the relevance of masturbation. Fright, excitement, and anxiety were the most potent of the exciting causes in Gowers’ view, of which fright took first place. Emotion was felt to be most important in young adult females. Trauma was included as an exciting cause of idiopathic epilepsy, second only to psychic causes in frequency, and not “organic epilepsy” in most cases where it results in no

lesion. Of the acute infections, Gowers singled out scarlet fever, which he considered especially neurotoxic. Gowers also pointed to “reflex causes” by which he meant causes mediated by irritation of peripheral nerves, visceral or external, and these can excite convulsions which may continue as persistent epilepsy: pain, digestive derangement, or an “anomalous or indigestible meal . . . In many cases of tubercular meningitis, the first symptom is a convulsion apparently induced by an indigestible meal.”

The “organic epilepsies” (as opposed to “idiopathic epilepsies”) were defined as the epilepsies associated with the “many organic diseases of the brain,” which Gowers does not go on to list. These are today what would be called the symptomatic epilepsies, and did not attract much interest in Gowers’ time.

Finally, Gowers made a unique contribution to “cause” in epilepsy with his theory that

the malady is self-perpetuating; when one attack has occurred, whether as the result of an immediate excitant or not, others follow either without any immediate cause, or after some very trifling disturbance . . . The search for the causes of epilepsy must thus be chiefly an investigation into the conditions which precede the occurrence of the first fit.

This concept (“seizures beget seizures”) continues to stimulate debate.

## Heredity as a cause of epilepsy 1857–1907: degeneration, and the neurological taint

As was made clear by Gowers, heredity was considered a leading etiological influence of the time. To understand what was meant by “heredity” in this period, the central importance of two related concepts, “degeneration” and the “neurological taint,” must be appreciated.

In the early and mid nineteenth century, particularly amongst French writers, the concept of degeneration (*dégénérescence*) replaced the supernatural as the main focus of interest in the causation of epilepsy. Theories of degeneration can be traced back to Ancient Greece, but formal scientific study developed in relation to the concept of speciation. Buffon the French naturalist suggested that living forms could be subject to degeneration (Buffon 1780), and the theme was taken up in relation to art, social science, and politics in the Romantic Movement. In the clinical field, the French psychiatrists, with their practice rooted in institutions, began to develop theories relating to mental and physical degeneration in mental disorders. In 1857 and 1860, Bénédict Morel published his two classic books on the degenerations of the human species and degenerations in mental disorders (Morel 1857, 1860) and these books became standard texts and were widely influential in medicine and beyond. Medical conjectures of degeneration were really part of much wider public concerns about social disintegration and the collapsing state of European cultural identity. There were fears that the rapid urbanization and population

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growth amongst the peasant and lower classes would sap national intelligence and morality. This was also reflected in the artistic movements of the time, and in studies of criminality and social science. Linked to ideas of *dégénérescence* was the concept that there existed a *neuropathic taint* (also known by various other terms including neurological taint, neuropathic trait, neuropathic predisposition). According to this theory, a wide range of conditions including epilepsy were inherited together. These conditions were not well defined, and different authorities incorporated different categories, but at their core these included, in addition to epilepsy: insanity, psychiatric disorders of various types, mental retardation, general paralysis of the insane, and locomotor ataxy; also moral degeneration such as was found in alcoholics or the criminal; and sexual degeneration evinced by masturbation, perversion, and sexual excess. This belief was widely accepted amongst neurologists, but Jackson earlier had opposed the idea of mixing up conditions with “no evident pathological connection.” According to Morel, this inherited tendency resulted in a *progressive* deterioration (degeneration) physically, mentally, and morally, over generations, and this tendency becomes progressively more severe, eventually resulting in the extinction of the line. At about the same time Jacques Joseph Moreau, a student of Esquirol, published his influential text *La Psychologie morbide* (1859) in which he introduced the category of the “neuropathic family,” in which hereditary mental disorders were passed down the ancestral line. Epilepsy was central to both Morel and Moreau’s writings, and was at the core of the “degenerative endowment.” According to these theories, the endowment might for instance cause mild hysteria in one generation, then a more serious epilepsy in the next, and dementia or idiocy in the next. The topic was further developed by Valentine Magnan, a pupil of Morel, and Jules Falret (1864), and ultimately by Charles Féré who divided the “neuropathic family” into a psychopathological arm which included epilepsy and the major psychiatric disorders, and a neuropathological arm which included chorea, migraine, and Parkinson’s disease (Féré 1884).

Interestingly, Moreau also included “genius” as a neuropathic feature, and believed that there was a “community of origin” for genius and madness. This was a concept which had its origins at least since Robert Burton’s *Anatomy of Melancholy* published in 1621, and was to presage the work of Lombroso who wrote “The creative power of genius may be in the form of degenerative psychosis belonging to the family of epileptic affections” (Lombroso 1889), and later similar pronouncements by Spratling and other stalwarts of the epilepsy establishment.

In parallel to the studies of mental degeneration were investigations of physical stigmata, and particularly physiognomy (Fig. 1.5). The study of physiognomy had a long tradition dating from Ancient Greece, and was considered so subversive that it was banned from university study in England in 1551 by Henry VIII. As a topic of social and medical interest, it had a resurgence in the 1770s following the work of Casper Lavater and Sir Thomas Browne. In psychiatry, an

important landmark was the publication of *Mental Maladies* by Jean-Étienne Dominique Esquirol (1838) who found that the insane and the retarded had specific physical appearances which reflected their degenerative taint. Moreau, Falret, and Magnan developed these concepts further.

The notion of degeneration was also linked in this period to the concept of atavism, which had biological plausibility given the theory of recapitulation popularized by Haeckel in 1866 (“Ontogeny recapitulates phylogeny,” a theory actually first proposed by Serres in 1824). Degeneration was thought to bring out atavistic characteristics (physical, behavioral, and mental) which were therefore the signs of the degenerative tendency. Epilepsy was seen as one symptom of degeneration, atavistic in nature, in the progressive downward degenerative spiral.

By the end of the nineteenth century almost all writings on the inheritance of epilepsy (of which there were a great number) accepted this concept. Amongst the major writers of the time, Echeverria (1873) reported a heritability rate of epilepsy in 25%, Déjerine (1886) of 66.8% when including other conditions of the neurological taint, Binswanger of 36.3% (1899), and Spratling (1904) of 56.0%. Turner (1907; see below) whose thinking on the topic was a great deal clearer than others, wrote: “in order to ascertain how far definitely neuropathic maladies play a part in the causation of epilepsy, the following table has been constructed to show the percentage frequency of the three main hereditary factors in the ancestral history of epileptics, viz. epilepsy, insanity, and parental alcoholism” (Table 1.3).

## Cesare Lombroso

The theories of the neurological taint and degeneration evolved furthest with the writings of Cesare Lombroso on criminality. Lombroso was a physician and psychiatrist by training, and is credited with the first scientific writings on criminality. His scientific method was “measurement” of both physical and mental features. His most enduring work was *L’uomo delinquente* (*Criminal Man*; published in five editions between 1876 and 1896/7) and *Criminal Woman* (*La donna delinquente e la prostituta et la donna normale* (Lombroso and Ferraro, 1893) which are packed with statistical tables of numerous measurements (this cult of anthropomorphic measurement was pioneered by Galton and Pearson, became a fundamental tool of the eugenics movement, and culminated in the anthropometry of the Nazi physicians). In these works, epilepsy was linked to criminality (an idea explored most fully in the fourth edition of *L’uomo delinquente* in 1889), a concept already widely written about in the previous decades (for instance by Echeverria and Maudsley). Lombroso’s theory of criminality was based on the demonstration that two-thirds of dangerous criminal individuals were “born criminals” who inherited a criminal trait and possessed “anomalies” (physical and psychological) resembling the traits of primitive man and animals (and even plants).

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**Fig. 1.5.** The “faces of epileptics” from the work of Cesare Lombroso, illustrating his physiognomic research. Lombroso (1835–1909) was professor of forensic medicine and hygiene and later professor of psychiatry and criminal anthropology in Turin.

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**Table 1.3** The table constructed by Turner (1907) showing “The percentage frequency of epilepsy, insanity and alcoholism as hereditary factors in the causation of epilepsy”

	Déjerine (1886)	Binswanger (1899)	Spratling (1904)	Doran (1903)
Epilepsy	21.2%	11%	16%	19.3%
Insanity	16.8%	29.6%	7%	7.9%
Parental alcoholism	51.6%	22%	14%	21.6%

Thus criminals were *atavistic throwbacks* to a primitive stage in human evolution. In his earlier work, he linked criminals with the insane and later with alcoholics, but in the fourth edition of his book turned his attention to epilepsy. He expressed the view that epilepsy was an atavistic characteristic and a fundamental component of the criminal type. He supported this by showing that criminals and epileptics shared the same physiognomy, physical and psychological features, and moral deficiency (Lombroso’s list from the fourth and fifth editions of *L’uomo delinquente* is shown in Table 1.4). Lombroso held the same view about epilepsy in females (although the prevalence of crime was less, due to the fact that the female cortex “although as irritable as men’s in its motor centre, is much less so in the psychological centres, precisely because there are fewer of these”). Moral insanity, criminality, and epilepsy were closely linked in women, as in men, and as Lombroso wrote about female criminals “I have always been able to find the signs of epilepsy, as in male born criminals.” Overall, he wrote that 26.9% of all epileptic men and 25% of all epileptic women have a “full criminal type” from the physiognomic point of view.

Lombroso went further, and suggested that some criminals exhibited “hidden epilepsy” (*epilessia larvata*) manifest by “sharp, sudden outbursts . . . the psychological equivalents of physical seizures, marked by unpredictability and ferocity”; and that this hidden epilepsy was responsible for criminal acts, especially acts of physical or sexual violence (this notion became widely accepted, and a classic example of hidden epilepsy is in the character and crimes of Roubaud and Lantier in Zola’s *La Bête humaine*, which was greatly influenced by Lombroso’s work). In addition to this association with criminality, Lombroso also associated epilepsy with genius (at one point he wrote that all geniuses were epileptic). The association with criminality and genius, two extremes of behavior, was an attempt to explain deviation from the norm in biological terms. Lombroso was a liberal and respected thinker, the leading Italian intellectual of his time, and this view of epilepsy reflected the mountain of stigma which epilepsy carried at the time. His work was widely discussed by the general public. It formed the basis of famous novels (not least by Huysmans and Zola, whom Lombroso even argued was epileptic himself). Lombroso’s theories of criminality had a profound influence on social theory for at least the next half century, and his lasting legacies are the medicalization of aberrant behaviors

**Table 1.4** Lombroso’s list of anomalies shared by epileptics and criminals

Skull	Abnormally large, microcephaly, asymmetric (12–37%), sclerosis, med. occ. fossa, abnormal indices, large orbital arches, low sloping forehead, wormian bones, simple cranial sutures the following characteristics shared by criminals and the morally insane
Face	Overdeveloped jaw, jutting cheekbones, large jug ears, facial asymmetry, strabismus, virility (in women), anomalous teeth
Brain	Anomalous convolutions, low weight, hypertrophied cerebellum, symptoms of meningitis
Body	Asymmetrical torso, prehensile feet, hernia
Skin	Wrinkles, beardlessness, olive skin, tattoos, delayed gray hair/balding, dark and curly hair
Motor anomalies	Left-handedness (10%), abnormal reflexes, heightened agility (16%)
Sensory anomalies	Tactile insensitivity (81%), insensitivity to pain, overly acute eyesight, dullness of hearing, taste, and smell
Psychological anomalies (% in epileptics)	Limited intelligence (30–69%), weak memory (14–91%), hallucinations (20–41%), superstitious, blunted emotions, love of animals, absence of remorse, impulsivity (2–50%), cannibalism and ferocity, pederasty (2–39%), masturbation (21–67%), perversity (15–57%), vanity, sloth, passion for gaming, mania/paranoia, delirium, dizziness, delusions of grandeur (1–3%), irascibility (30–100%), lying (7–100%), theft (4–75%), religious delusions (14–100%)
Causes	Heredity (of alcoholism, insanity, epilepsy, old parents), alcoholism

Note:

List is from editions 4 and 5, with percentages quoted by Lombroso from his own work or that of Cividalli, Tonnini, and Bianchi.

and the demonstration that social behavior had a biological basis. These themes have been the focus of research ever since; perhaps no more so than now.

## Reflex theories of causation

The term *reflex epilepsy* also has its roots buried deeply in the historical thought on epilepsy. Galen referred to “sympathetic” epilepsy in which the cause was outside the nervous system and similar concepts have been long prevalent. Marshall Hall

and Brown-Sequard preceded Jackson in exploring reflex mechanisms, and Reynolds and Jackson widely discussed the “reflex” theories of causation of epilepsy. The interest in “reflex seizures” in those days was a general interest in the possibility of reflexes underlying epilepsy, rather than in the narrow meaning of reflex seizures today. According to Jackson, “irritation” (of various types) could trigger seizures by draining the cerebral centers of their energy. The irritation could arise in the periphery, ears, eyes, teeth, digestive tract, or sexual organs. These conditions were sometimes classified as “sympathetic epilepsies” – in the sense that they were due not to a primary disorder of the brain but rather to a systemic irritation that triggered a seizure.

In the latter part of the century, a particular and common reflex cause was considered to be eyestrain, particularly in the American literature. Treatment was with eyeglasses and tenotomies (this is well discussed by Friedlander 2001). Other reflexes were induced by pain in a limb, by genital stimulation, and by pathologies in the ear or nose. Gowers in 1881 and 1901 includes pain and gastrointestinal disturbance within his category of reflex epilepsy, but nothing else. Turner (1907) recommended surgical excision of traumatic lesions of the peripheral nerves, removal of a tight prepuce in boys, treatment of coexistent diseases of the ears or nasopharynx and removal of foreign bodies, adenoid growths, and polypi to remove the reflex stimuli. He also mentioned that errors of refraction could be corrected and glasses worn, in view of the dramatic results of such treatment by Dodds, Gould, and Féré, but one senses a lack of enthusiasm about this senseless therapy.

Perhaps because of these obvious absurdities, the reflex theories fell out of fashion in the early twentieth century. However, Pavlov’s demonstration of conditioned reflexes reignited interest in the possibility of epilepsy being a reflex phenomenon and Pavlov’s theories were favored as the pathogenic mechanism, for instance, in the influential paper on musicogenic epilepsy by MacDonald Critchley (President of the International League Against Epilepsy [ILAE], 1949–53) in 1937. As time passed, the term reflex epilepsy began to refer to very specific sensory precipitants and acquired a meaning not dissimilar to that of today, referring largely to rare and curious cases.

### Auto-intoxication

By 1900, a second widely held explanatory model of causation was gaining momentum – the theory of “auto-intoxication.” According to this theory, epileptic seizures were caused by toxins produced within the person’s own body (not dissimilar to Galen’s theory of humors). Most believed that these toxins arose in the bowel, either through fermentation or from bacteria. This was backed up by reports for instance of sigmoidoscopy showing “acute angulation of the sigmoid colon” and “impaction of the sigmoid of an inordinate character” (Axtell 1910), and by radiological examination with bismuth showing

“coloptosis” (Clark and Busby 1913; cited by Friedlander 2001). Experiments, which included the injections of blood from epileptic patients into rabbits, or intraperitoneally in guinea pigs, producing “violent convulsions,” gave further credence to the auto-intoxication theories. Amongst the toxins actually responsible, much was written about uric acid. As a response to these theories, it was a short step to colectomy as a treatment of epilepsy, discussed further below.

### Organic brain disease

During this period, the focus on theories of causation of epilepsy was not on organic brain diseases as such, but on predisposing and exciting factors, on Jackson’s emphasis on mechanisms (vascular and nutritive), and on theories of inheritance, degeneration, reflex epilepsy, and auto-intoxication. Indeed, the epilepsies due to organic diseases of the brain (organic epilepsy; symptomatic epilepsy as it is known today) were often considered not “true” epilepsy. All however recognized that cerebral disease could cause epilepsy, and indeed following Jackson that its location determined the nature of the epilepsy. This lack of interest partly reflected the lack of investigatory tools (only postmortem and surgical neuropathology provided any help here) and also the lack of a systematic classification of the degenerative and particularly pediatric conditions. Neuropathology had identified, however, a number of organic disorders that were shown to have some sort of causal relationship with epilepsy. Of these, widely accepted were the developmental disorders (including porencephaly, heterotopy, microcephaly, and brain hypertrophy), asphyxia at birth, infantile hemiplegia and cerebral palsy, brain tumors, cerebral trauma causing a cicatrix, cerebral infection such as abscess, and degenerative conditions resulting in softening of the brain or other pathological findings.

### William Aldren Turner 1907

Turner published his classic text on epilepsy in 1907 (Turner 1907) and devoted two chapters to the topic of etiology. These represented the advanced opinion of the day.

First discussed was heredity. Turner (Fig. 1.6) pointed out the difficulties in ascertaining this, citing problems in obtaining family histories and the inclusion of conditions which “do not stand in any causal relation to epilepsy, but are merely thrown in occasional connection with it, such as, tuberculosis, gout, and rheumatism.” Turner differentiates these latter conditions from those of the “neuropathic disposition.” However, Turner found that the most common feature of the neuropathic trait in an ancestral line of epileptics was epilepsy itself. Amongst his 676 epileptic patients, he found that 37.2% had a family history of epilepsy, and only 3.1% a family history of alcoholism, 5.4% of insanity, and 5.3% a family history of other neurological disorders of relevance (“nervousness,” migraine, deaf-mutism, etc.); 49.0% had no known heredity factor. As Turner wrote:

## Section 1: Introduction



**Fig. 1.6.** William Aldren Turner (1864–1945) was appointed as full physician to the National Hospital Queen Square in 1900 and visiting physician to the Chalfont Colony in 1902.

*Although epilepsy and insanity are the two main elements of the psychopathic hereditary degeneration, the existence in the family history of hysteria, chorea, the drug habit, migraine and paroxysmal headache, are important not so much from any direct bearing which they may have upon the development of epilepsy, but as indications, to some extent, of the neuropathic tendencies of a family. We find such disorders not uncommon in the family and personal histories of epileptics but it is difficult to prove that their occurrence is specially frequent.*

The signs or “stigmata” of degeneration detected by Turner in his epileptic patients included: facial deformities (inequalities of the two sides of the face, irregularities of the nose, prognathism or arrested development of the lower jaw), deformities of the hard palate, dental abnormalities, deformities of the ears, deformities of the iris, abnormal arms, mental aberrations, stammering, and astigmatism. Amongst his own patients, the frequency of such stigmata was 66.5%, and Turner believed these signs were evidence of the “neuropathic disposition.”

As he wrote in conclusion:

*it is therefore obvious that in the majority of cases of epilepsy, no external exciting cause of the disease is necessary. Many conjectural explanations are given by the patient or his friends . . . [e.g. trivial head injury, sunstroke] . . . the real explanation is to be found in the rapid brain growth during the first few years of life, the onset of puberty and the full development of the reproductive organs, in*

*persons anatomically predisposed by heredity to nervous instability and convulsions . . . It has also been shown that structural stigmata of degeneration, more particularly of the face, teeth, palate and ears, are frequent phenomena in the subjects of epilepsy, and that their presence is of great importance in determining, not only the degree of inherited predisposition, but also the severity of the disease.*

Turner considered that the majority of cases were due to this “predisposition” (usually hereditary) and that an “exciting cause” was present in a minority of cases. The common “determining causes of epilepsy” (the exciting causes) were in his experience:

- (1) Physiological causes – puberty, menses, pregnancy, puerperium, lack of sleep, ingestion of certain foods.
- (2) Psychical causes – shock, emotional excitement, fear, anxiety, overwork.
- (3) Pathological causes – exanthemata and acute infective diseases, organic diseases of the brain and trauma to the head, reflex epilepsies due to morbid conditions of various other organs, auto-infection from the alimentary canal, disorders of bodily metabolism and cerebral palsy.

In Turner’s personal case series, psychical causes accounted for 4.1%, head trauma for 7.2%, acute infective causes for 5.6%, syphilis for 0.4%, and “cerebral birth palsy” for 5.9%.

Another important thread within Turner’s conception of cause was the fact that once a fit had occurred, an “epileptic habit” is in danger of developing and thereafter fits occur even in the absence of any exciting cause – and here he is following Gowers. Because of this, early and immediate therapy was mandatory, and as Turner showed, many cases of early epilepsy if treated promptly do not go on to develop a chronic condition.

## Theories of the causation of epilepsy 1907–1960

In the early part of this period, there were few lasting contributions to the study of etiology in epilepsy. The world was possibly represented greater challenges to the ingenuity of humankind. In the world of epilepsy, therapeutic advances greatly outstripped interest in causation – and this was a period of major discovery in the fields of antiepileptic drugs and also neurosurgical therapy.

### Auto-intoxication

In the early part of this period, interest in the auto-intoxication theory of causation gained momentum and in particular the view that epilepsy (and other conditions such as psychosis) was the symptom of low-grade infection, somewhere in the body. The gastrointestinal tract was the favored site and surgical resection of various parts of the gastrointestinal tract began to flourish. One illustrative, if extreme, enthusiast was the psychiatrist Dr. Henry Cotton who became superintendent of Trenton State Hospital in 1907, a residential institution for mentally handicapped, epileptic, or psychotic patients. He decided to