# CHAPTER 1

# The concept of status epilepticus and its history

*If the possessing demon possesses him many times during the middle watch of the night, and at the time of his possession his hands and feet are cold, he is much darkened, keeps opening and shutting his mouth, is brown and yellow as to the eyes... It may go on for some time, but he will die.*

(XXV–XXVIth tablet (obverse) of the Sakikku cuneiform[1], 718/612 BC)

## Pre-history of status epilepticus

Epilepsy, that unrivalled hierophant of neurology, has an ancient pedigree. The Sakikku cuneiform is the earliest known record, and there, with due foreboding, is the first allusion to status (fig. 1.1). Surprisingly, though, in the long line of historical reference to epilepsy which followed, status received scant attention. No condition resembling status was recorded by Hippocrates in the fourth century BC in his great work on epilepsy, nor by Galen in the second century. The fifth-century Numidian, Caelius Aurelianus, gave a grave prognosis to protracted epileptic attacks 'which extended into a second day', but there was little other mention of prolonged seizures in the classical literature. Mediaeval medicine left status undisturbed, although epilepsy was extensively described because of its demoniacal associations. In renaissance times there were sporadic reports:

the illustrious cardinal Commendoni suffered sixty epileptic paroxysms in the space of 24 hours, under which nature being debilitated and oppress'd he at leangth sank, and died. His skull being immediately taken off, I found his brain affected with a disorder of the hydrocephalous kind.

(Gavassetti 1586)

. . . whenas fits are often repeated, and every time grow more cruell, the animal function is quickly debilitated; and from thence, but the taint, by degrees brought on the spirits, and the Nerves serving the Praecordia, the vital function is by little and little enervated, till at length, the whole body languishing, and the pulse loosened, and at length ceasing, at last the vital flame is extinguished.

(Thomas Willis 1667)[2]

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After the mid-eighteenth century, more clinical observations were made of status, cases which were generally considered to be isolated curiosities (see Lysons 1772, Heberden 1802, and Good 1822 cited by Hunter 1959/60). It was only in the nineteenth century that status was clearly differentiated from the ordinary condition. The expression *état de mal* is first found in the University Dissertation of Louis Calmeil (1824)[3], where the term, coined by the patients themselves, was said to be common currency in the Bicêtre and Salpêtrière (see also Bouchet & Cazauvieilh 1825/6; Beau 1836) and how strangely appropriate it is that status should be christened in that 'museum of living pathology', so important to the history of epilepsy. The first appearance of the latinised English expression *status epilepticus* was in Bazire's translation of Trousseau's lectures on clinical medicine in 1867 (Trousseau 1868*a*,*b*).

Why, in contrast to epilepsy, was status so infrequently recorded, and so long in its recognition? Hunter (1959/60)[4] speculates that the condition was actually rare before powerful anticonvulsant drugs became available (bromides were introduced into clinical practice in 1857), and that the condition had become common due largely to the risks of sudden anticonvulsant drug withdrawal; a view that can be only partly substantiated, as many drug-naive patients presenting with status are encountered today. Status may have increased in frequency from the mid-nineteenth century, however, and it would be an irony indeed if this 'maximum expression' of epilepsy was in fact caused by its treatment.

## Origins of status epilepticus

When Calmeil defined the term, status epilepticus was a condition barely recognised, probably rare, and not differentiated from the greater subject of epilepsy. Within a few years, however, began a growth in conceptual thought which has continued to the present day. This evolution can be divided conveniently, albeit artificially, into three phases, the first of which is that of classical description. Research was concentrated upon accurate clinical and pathological description; to this period we owe meticulous observations of individual cases, and the establishment of classical histology and morbid anatomy. The underlying assumption that status was simply a severe form of repetitive epilepsy was rejected, and the condition was viewed rather as a separate entity, 'a maximum expression of epilepsy', with clinical features distinct from ordinary seizures. The term was confined to grand mal status, and although other forms of continuing epilepsy had also been recognised these were not categorically linked. Rudimentary drug treatment was now possible – as always, a potent stimulus to research. The second phase was ushered in by the discovery of electroencephalography (EEG) in 1924 by Berger[5]. That single invention changed profoundly the theoretical basis of epilepsy and of status. EEG dominated research on status for the next four decades. During this time, the electrographic correlates of status were described and the basic neurophysiological principles of epilepsy established. Other clinical and experimental research was carried out, but was mainly subservient to EEG. Treatment was also advanced. The Marseilles Colloquia of 1962 and 1964 (of which
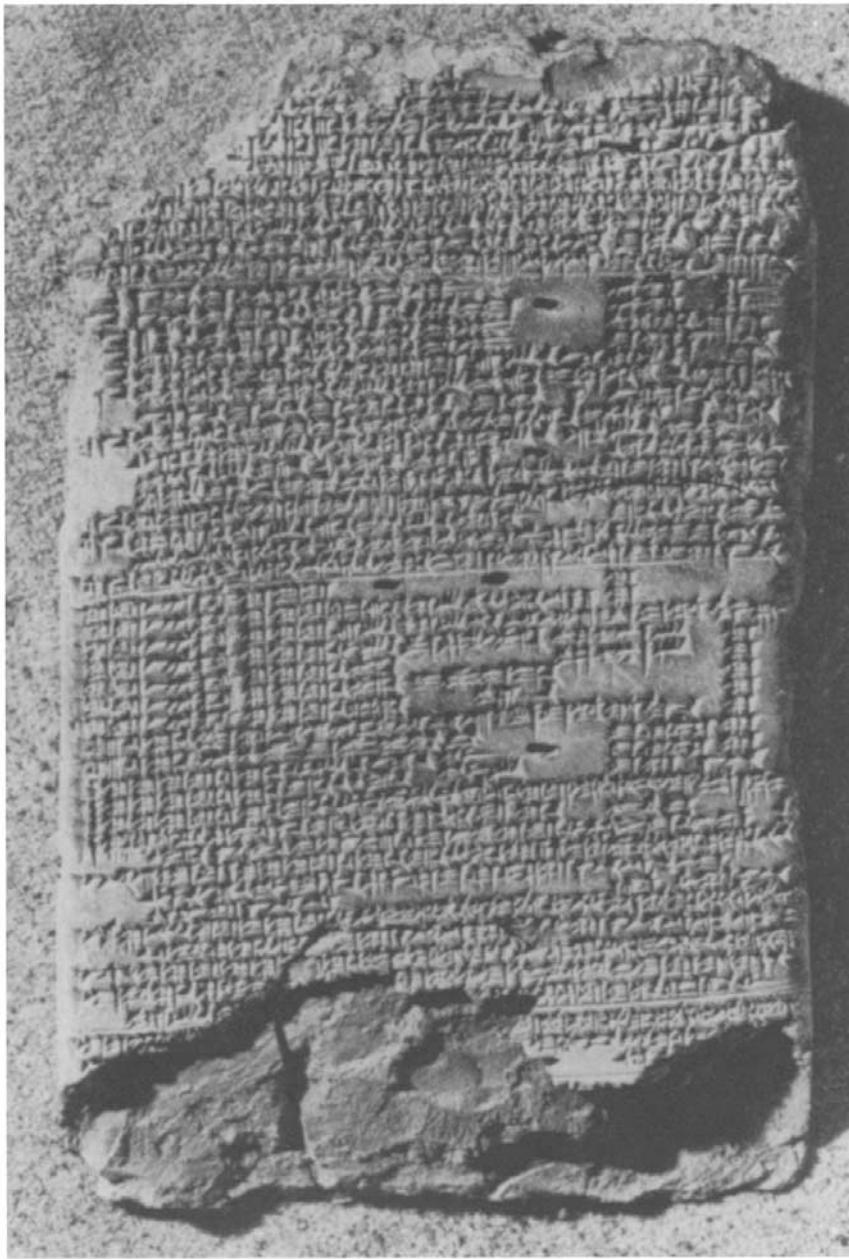
**Fig. 1.1.** The Neo-babylonian cuneiform (tablet BM 47753 obverse) showing the text of the XXV/XXVIth tablet of Sakikku (all diseases), which contains the first known reference to epilepsy and to status epilepticus. (From Kinnier Wilson & Reynolds 1990, with kind permission.)

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more later) were landmarks in this evolution, and at these conferences definitions and classifications of seizures and of status were proposed, heavily influenced by EEG. Here was made implicit the concept that status was simply iterative seizures, rather than a specific entity (a return to pre-nineteenth century thought). The definition of status was also widened to include iterative versions of other seizure types (a logical step given the nosological basis), and the view was established that there are *as many types of status as there are types of seizure*. There was a relative neglect of other aspects of status, particularly study of its basic mechanisms, aetiology and anatomy. In the succeeding years, a third phase of activity has begun in which pharmacology, neurochemistry and experimental physiology have increasingly replaced human EEG as the focus of status research, and great advances in treatment have also been made. The clinical concepts of status have again expanded to include conditions crossing seizure type boundaries, and the utility of underpinning classification on the basis of seizure type is being challenged. New imaging methods have revived interest in the structural and anatomical basis of status, and in developmental aspects. Status is now again increasingly seen as an entity distinct from other seizure types. These topics form the substance of this book.

Before proceeding to these modern developments, though, in the rest of this chapter, the two earlier phases are discussed, some classical descriptions given, and the history of definition and classification traced from the Marseilles Colloquia; the current conceptual basis of status can best be understood in the context of such an historical approach.

## Classical descriptions of status epilepticus

Modern neurology can be said to have emerged in the mid-nineteenth century, in London and Paris, with epilepsy its mystagogue. This was the age of meticulous scientific observation, made possible in epilepsy by the establishment of asylums and hospitals in which great numbers of epileptics were confined (Temkin 1971). In England, asylums for the mentally ill had existed at least since 1547 (when the hospital of St Mary of Bethlehem was incorporated as a royal foundation for the reception of lunatics; the famed 'Bedlam'), but such institutions specifically excluded sufferers from epilepsy. In the nineteenth century, attitudes changed, and epileptic cases were admitted first to county asylums, and then to the metropolitan institutions. It was the newly opened *National Hospital for the Paralysed and the Epileptic* that proved the most fertile ground in this golden age for epilepsy research. Here physicians such as Jackson, Ferrier, Gowers, Horsley, Sieveking, Turner and Colman saw and described cases of status[6]. In Paris, the Salpêtrière, the biggest asylum in Europe (housing up to 8000 persons in the eighteenth century when the total population of Paris was only 500 000, and 5000 persons in Charcot's time), and its sister institution the Bicêtre admitted epileptics from the early nineteenth century. In 1813, there were 389 epileptic women at the Salpêtrière and 162 epileptic men at the Bicêtre, but by the middle of the century these numbers had grown enormously. Esquirol, Calmeil, Pinel, Charcot and

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Bourneville all cut their epileptic teeth at these institutions, and throughout Europe alienist physicians led this developing field.[7]

To Paris went the privilege of bringing status into the modern world, for it was here that Bourneville[8] at the Bicêtre, and Trousseau [9] at the Hôtel Dieu recorded the first clinical descriptions of status. Desiré Bourneville, favoured pupil of Charcot, published his celebrated paper in 1876. *Etat de mal* was defined as a 'serious complication' of epilepsy, distinguished by five characteristic features: (1) the repetition, more or less incessant, of seizures that in consequence often became subintrant; (2) collapsus, which varied in degree of severity from transitory loss of consciousness to complete and irreversible coma; (3) hemiplegia, more or less complete, but transitory; (4) characteristic rates of pulse and respiration; and (5) marked rise in temperature, persisting in intervals between seizures and intensifying after the seizures ceased. From personal observation, he recognised convulsive status to be an entity with 'progressive clinical stages', a concept only recently rediscovered (see pp. 53–4 and pp. 61–6), and his observations on temperature (his primary interest), pulse and the systemic effects of status have not been bettered.

He detailed the status in the case of Marie Lamb . . ., an epileptic hemiplegic and retarded girl of 19 years, in the Salpêtrière, starting on 8 June 1874 (Bourneville 1876). This is worth quoting at length as a masterful depiction of secondarily generalised tonic–clonic status, and a classic instance of meticulous observation. On the previous day Marie had had her habitual seizures at increasing frequency (17 in all). On the morning of 8 June, the seizures began to occur in series of three initially with consciousness intervening, but by 10.45 a.m. consciousness was lost, there were 17 seizures in 1¼ hours, her pulse rate was 128/minute and vaginal temperature 39.3 °C; status had occurred. Bourneville identified three phases in each seizure:

> In the first phase – initiation – the legs, more so the left, were flexed slowly
> over the thighs and the patient uttered a kind of grunt, then several
> raucous cries in succession. In the second phase, her eyelids were closed;
> when opened, her eyes were seen to be strongly deviated to the left, and
> her face turned less sharply in the same direction; within four or five seconds,
> her eyes and face turned to the right; her left arm lay flexed and rigid
> across her body, the fingers tightly flexed across the thumb; her right arm
> was also stiff, but extended and raised 20 or 30 cm above her body, the fingers
> flexed but alongside the thumb; the lower limbs remained flexed and rigid.
> The third phase was marked by very strong and rapid convulsions of the
> right facial muscles, followed in several seconds by convulsions of the eyelids
> and the left frontalis; the mouth was deviated to the extreme right, the right
> nasolabial furrow strongly accentuated, the left obliterated; at the same time,
> clonic jerks of moderate intensity were observed in the lower limbs, more so
> the right; breathing was stertorous and there was much frothing at the mouth.

Bourneville noted certain modifications of this pattern in subsequent seizures:

> at the onset, flushing of the face; in the second phase, an asymmetry of the
> eyelids, the right closed, the left half-open; in the third phase, more

> violent clonic jerks, the face purple and covered with sweat, more marked
> on one side than the other, with urinary incontinence.
>     Treatment was given with 'sinapismes, lavement purgatif' and quinine
> sulphate – to no effect. Between midday and 6.00 p.m., a further 122
> seizures were recorded and another 7 between 6.00 and 6.30. Leeches were
> applied behind each ear and ammoniac inhalations administered. The
> patient moved her head, opened her eyes and moaned several times, as
> though waking. At 7.00, the pulse rate slowed from 124 to 100 and the
> temperature had fallen to 39.8. Treatment with quinine sulphate and
> ammoniac inhalations was continued. In the next two hours, two further
> seizures were recorded, bringing the total number over the 24 hours to
> 9.00 p.m. on June 8 to 168. Another 20 were recorded overnight, to
> 6.00 a.m. At intervals around midnight, the patient had become
> semi-conscious; she had seemed to recognise the nurse and had swallowed
> two spoonfuls of soup. At 9.00 a.m., the patient shook her head when an
> attempt was made at ophthalmoscopic examination and she moved her left arm;
> she opened her eyes from time to time; her gaze was dulled, and eyes and
> face turned mostly to the left, the pupils equal and constricted; a very
> fine nystagmus could sometimes be detected; her lips, gums and tongue were
> dry. The left arm was held above the bed, while the right arm was now
> completely flaccid, as were both lower limbs, more so the right. Pinprick
> repeated rapidly over all four limbs produced grimaces and sometimes little
> moans; when the face was pricked, the grimaces intensified. The pulse rate
> had now risen to 146, small, regular and readily palpable at the wrist;
> respirations were 60 per minute and (vaginal) temperature 40.6. By 11.00 a.m.
> no further seizures had been recorded but slight convulsive movements were
> noted from time to time in the limbs. Three hours later, the coma deepened;
> the skin had now taken on a yellowish pallor and breathing had become
> stertorous. At 4.00 the following morning, the patient died.

At autopsy on 10 June, the brain was found to be grossly abnormal, showing marked asymmetries, softening, swelling, atrophy of Ammon's horn and sphe-noidal convolutions, and right hemisphere hemiatrophy and cavitation. Bourneville identified two periods in this case, as in the majority of cases of status: the convulsive and the meningitic. In the convulsive period, the increasingly rapid succession of the series of seizures, associated with a rise in body temperature, heralded the second. The two periods could, as in this case, be separated by some sort of temporary respite. The meningitic period might be brief or prolonged. It might be marked by decubitus, by violent agitation, or by contracture; the one constant feature was a dramatic rise in temperature. Temperature therefore should be regarded as the principal prognostic sign. The clarity and succinctness of this meticulous description earned Bourneville the Prix Godard of the Société de Biologie.

Trousseau (1868*a*,*b*) at the rival hospital of the Hôtel Dieu had explored, sys-tematically, the various forms of epilepsy in his clinical lectures published 8 years before Bourneville's essay, and again recognised the special nature of status. He distinguished ordinary seizures from those 'which are repeated in rapid succession

and end in the death of the patient' – true status epilepticus. He noted changes in the patterns of convulsions during status, and concluded that:

> in that form of status epilepticus where the convulsions are practically continuous something specific happens which demands an explanation. The patient is in the throes of his grand mal seizures; then, in a second or two, he has a slight convulsion in his face, in his neck or his limbs, a convulsion which is very fleeting, barely visible but which is repeated thus in 2, 3, 4 or 5 hours. A convulsive seizure is certainly continuing; but it is important to note that this is no longer a [simple] grand mal seizure; that it is something very different, something quite special, which is dependent on the particular state of irritation of the brain and spinal cord.

Trousseau also observed that petit mal seizures might, as with grand mal, occur with such frequency 'that one seizure would become confused with the next, simulating a continuous seizure which might persist for 2 or 3 days'; this was petit mal status, in the same sense, argued Trousseau, that convulsive status can be seen in patients with grand mal seizures (no further advances in this subject were made until Lennox uncovered the EEG pattern of petit mal). Indeed, as grand mal and petit mal seizures often occurred in the same individual, Trousseau considered the seizures to be variants of a single underlying diathesis, and strict differentiation was impracticable, a synoptical view of classification that anticipates the much more modern syndromic approach.

Although Trousseau identified petit mal status, his was not the first description of nonconvulsive status. Cases of epileptic fugue and furor, many of which were probably status, had interested physicians for at least the previous 100 years. Prichard[10] in 1822 wrote:

> epileptic delirium generally appears when the patient is expected to revive from the comatose state consequent upon a severe fit; but, in other instances, it appears without any fit. The face is flushed, and the aspect of the patient is like that of a man under intoxication; he attempts to start from bed and run about, and, on being witheld, vociferates and endeavours to overcome resistance. Sometimes the appearance of maniacal hallucination displays itself, but more generally the disorder resembles phrenetic delirium. It continues commonly one, two or three days, during which the patient requires confinement in a straight jacket, and then gradually subsides, and the patient returns to his previous state.

He also described epileptic ecstasy:

> a more unusual circumstance in the history of epilepsy is the appearance of a species of somnambulism, or of a kind of ecstasis, during which the patient is in an undisturbed reverie, and walks about, fancying himself occupied in some of his customary amusements or avocations.

Prichard documented cases, but did not link these to status; that distinction belonged to Sir Samuel Wilks, the great Guy's syphilologist (also the first systematically to employ bromides in the treatment of epilepsy). He recognised epilepsy

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to be characterised by two essential symptoms: complete loss of consciousness and convulsion. In grand mal status, both features were unmistakable. But there was also a condition associated with epilepsy, as Wilks saw it, in which neither could be detected:

> the patient is in the condition which is popularly called 'lost'; he is scarcely conscious of acts and conversation going on around him, and yet he may continue walking in a given direction, showing that his movements must still, in a measure, be guided by his senses. He is in a kind of dreamland, and is indeed in much the same state as a somnambulist. This condition, under many varieties of form, is called the status epilepticus, although the term is more usually applied to the case where the patient lies for a lengthened period in a kind of trance or stupor, as, for example, in the case of a man lately in the hospital, who, after a succession of fits, lay for hours in a state of lethargy. In the milder forms it is one of great interest from a physiological point of view and seems to point to the possibility of a subconscious state, in which the brain is sufficiently active to control the spinal system and yet not awake enough to excite the feeling of consciousness. In reference to the influence of the brain on the muscles and the necessity of consciousness to preserve their tone, the condition is one full of interest.
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> (Wilks 1878)

Epileptic fugue had been the subject of other sporadic reports; an early example was that of Bright (1831) of a child of about 12–14 years old: 'he became delirious, and wandered in the streets in a state of complete unconsciousness from Clapham Common to Shoreditch, and was between four and five hours on the road'; Bright also described patients dying after a succession of seizures without intervening recovery of consciousness. Perhaps the most celebrated epileptic fugue was that presented by Charcot, on 31 January 1888, of a Parisian delivery man who, in nonconvulsive status, had repeated perambulations across and outside Paris (see frontispiece), lasting days at a time. There were only islands of memory of events during the fugues, but passers-by were unaware of anything untoward; he awoke from one fugue to find himself swimming in the Seine. On compelling grounds, Charcot considered these episodes to be epileptic. Hughlings Jackson also described cases of prolonged psychomotor epilepsy (see Taylor 1931 and p. 116). Amongst the other forms of status recognised in the nineteenth century must be mentioned infantile spasm (West syndrome) which was accurately described by West in 1841, and then lay virtually undiscovered for the next 100 years (see pp. 42–3). Cases of what would now be considered the Lennox–Gastaut syndrome, febrile status, postictal confusion, and myoclonic status were described by Jackson and Gowers. Kojewnikoff's classic description of *epilepsia partialis continua* was published in Moscow in 1895 (Kojewnikoff 1895*a*,*b*) (see p. 85). The early pathological descriptions of patients dying in status and of epilepsy were made by Sommer (1880), Pfleger (1880), Chaslin (1889), Alzheimer (1898) and Bratz (1899), and are discussed in more detail in chapter 4. Thus, by the end of the nineteenth century, convulsive and nonconvulsive status were recognised, and their clinical forms and associations documented.

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In 1903, the era of the classic description can usefully be said to end with the writings of L. Pierce Clark[11] and Thomas P. Prout. The latter was a pathologist and the former an alienist, like Bourneville and others before him. Three papers were published in which the clinical and pathological appearances of status epilepticus were explored systematically in a series of 38 patients (Clark & Prout 1903/4). These descriptive papers on status are unequalled in breadth or perspicacity by any published before or since.

They formulated a definition of status, for the 'typical case': status epilepticus is the maximum development of epilepsy, in which one paroxysm follows another so closely that the coma and exhaustion are continuous between seizures. The state is almost always sooner or later accompanied by a marked rise of temperature, pulse and respiratory frequency, which is indicative of the degree of exhaustion. Their detailed clinical description is cited at length, for its discernment and accuracy, and in particular for its documentation of the natural course of status unaffected by antiepileptic drug treatment – an opportunity no longer with us, as modern treatment so profoundly alters the clinical appearance.

Two phases of grand mal status were notable, resembling the phases described by Bourneville, the first convulsive and the second stuporous. These were often preceded by a prodromal period in which could be noticed 'a steady increase in the paroxysmal frequency of seizures', 'a sort of pseudo-status' (the term is used currently in a different sense). They were 'the heralds; aborted, imperfect or incomplete status periods'.

The temporal pace of status was well observed. In the convulsive phase:

> Generally the attacks occur with an interval of one-half hour or a full hour at the onset. Each attack is complete and separate from its predecessor, keeping the peculiar individuality, common to each case of epilepsy. In Jacksonian, or better, partial epilepsy, the single seizure of the status holds to a distinct order of invasion, so long as exhaustion is not extreme and the definite order of muscular involvement is continued throughout the status. At first, consciousness is completely regained between paroxysms; a little later, as the periods between attacks shorten, consciousness is but partly regained, and finally the comatose state is not rallied from between attacks, and the stupor deepens into profound coma. In all cases in which a definite order of muscular involvement obtains, the subsequent coma is less profound and the status in consequence is less severe. As the attacks culminate in their greatest frequency, the period of rest between convulsions may be entirely omitted and some one part of the body may remain continuously in spasm; the part last involved in convulsion not ceasing from agitation before the muscles engaging in the initial stage of the next paroxysm begin again to sweep the rounds of the muscular invasion of the subsequent fit. The spasm may be incessantly clonic, or there may be a slight lessening of paroxysmal intensity, thus marking the end and the begining of isolated discharges; this overlapping is almost always seen in the convulsive stage of fatal status. With the increasing frequency of attacks the paroxysms usually diminish in intensity; the tonic period, if present at the beginning, may be obviated or omitted entirely in the advanced status. The paroxysms at the end of the convulsion

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> may be localized to a single muscle or a small group of muscles. Generally in status composed of fulminant convulsions, of general and simultaneous involvement, the end of the convulsive stage sees only slight general or fibrillary tremors throughout the whole body. As the exhaustion increases after the first few attacks there is elevation of temperature, increased pulse rate and respiratory frequency. The pulse and temperature may surmount to a great height, the temperature to 107 or 108 F., and pulse to 160 or 200 per minute. At last the convulsions lessen in frequency and the stuporous stage is ushered in with the coma of collapse, which picture is analogous to that of the coma of a dynamic fever, such as typhoid . . .
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> [The stuporous state] is but the resultant exhaustion from the convulsive stage; exhaustion, as it were, being piled on exhaustion. The mouth is foul, the tongue is dry and fissured, and the skin is covered with cold clammy sweat; swallowing becomes difficult or impossible. The urine is usually voided and stools may be passed involuntarily. The patient may die of asphyxia in the paroxysms, although as a general rule he passes a few hours in profound coma, in which stage, until death or convalescence, slight convulsive tremors may occur. Such convulsive phenomena are but mere phantoms of the former severe convulsions. Therefore one sees how purely arbitrary the clinical division of status into two stages may appear; in the one convulsion, and in the other coma, predominates. All the deep and superficial reflexes are abolished in the coma; the respiration becomes loud, noisy and stertorous in character; the temperature and pulse may undergo marked alteration depending upon the frequency and intensity of the foregoing symptoms. Death may terminate the stuporous stage at any time. If recovery is to occur, coma wears away, and is slowly replaced by stupor which in turn may be followed by mild delirium or hallucinations, which semi-exhausted state is finally replaced by a more or less rapid convalescence and the patient resumes the pre-status condition in a week or ten days. Generally, if recovery does not follow more or less promptly, a low muttering delirium supervenes, extensive sloughing of the nates follows and life itself is more or less suddenly terminated. The foregoing constitutes the usual clinical picture of a case of typical status epilepticus.

The duration of the episodes of status recorded by Clark & Prout was very variable, but most cases continued for 2–9 days, and prognosis was not related to duration (a view no longer tenable). They found, as their predecessors had done, that their 'typical' cases of status were characterised by specific clinical signs. Reflexes, deep and superficial, were lost 'as soon as the comatose stage in the convulsive period becomes continuous between paroxysms and invariably remain absent throughout the stuporous stage. They can again be elicited just before consciousness is regained; their return being often the first indication that consciousness will reappear'. Various changes in the eyes were noted. The pupils usually dilated during the early part of the convulsive period, contracting to normal after the paroxysms, but with deepening stupor they dilated and remained insensible to light. A change in the shape of the pupils, to an ellipse or 'wavy outline', at the onset of convulsions consisting of a general tremor was not unusual; they might also dilate with inspiration and constrict with expiration. A more or less

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